Variation in Visual Outcomes and Quality of Life in Patients with Neovascular Age-Related Macular Degeneration:

what does any variation mean?

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Abstract

Neovascular age-related macular degeneration (nAMD) represents one of the leading causes of blindness in both developed and developing countries. This thesis examines inequalities and variations in visual outcomes for people being treated for nAMD, the reasons behind any variation, and how this variation relates to self-reported quality of life.

nAMD began to be treated *via* intraocular injections with anti-vascular endothelial growth factors (anti-VEGF) after 2006. This thesis drew on the landmark trials that first established the safety and efficacy of anti-VEGF therapy for nAMD.

Using a systematic review, this thesis then investigated whether there were factors that could be identified from the literature that influenced how effective anti-VEGF therapy is in reducing visual loss in patients with nAMD. This thesis highlights the importance of being able to identify modifiable factors, such as number of anti-VEGF injections received, that could lead to better visual outcomes for these patients.

This thesis then goes on to examine levels of variation in visual outcome in nAMD nationally in the UK, as well as further investigating any influencing factors that could not be identified in the systematic review. This was done using a large real-world dataset of over 26,00 patients from seven hospitals. This highlighted significant levels of variation, but struggled to identify definitively further influencing factors, such as ethnicity or social deprivation. This could be because there genuinely was not an associated relationship between these factors and visual outcomes, but certainly in the case of ethnicity, it is particularly apparent that there was an overwhelmingly white population, so there may have not been enough ethnic variation to detect any effect of ethnicity.

This thesis then investigates the link between visual acuity and quality of life, in a prospective study of patients from a teaching hospital in York. However, due to a much-reduced sample size, partly due to the COVID-19 pandemic, this thesis was unable to meaningfully link the two outcomes.

The focus of this thesis was that of identifying and understanding variation in patients being treated for nAMD, within a wider picture of variation and inequality in healthcare in general. It showed variation in visual outcomes, but apart from visual acuity at baseline and number of injections, it was unable to identify other influencing factors. It is therefore concluded that further work with larger sample sizes needs to be undertaken to definitively address the overall aims of this thesis. Along with this, further attention needs to be given to the role of intersectionality of possible influencing factors in visual outcomes. Some of the methodology used in this thesis also need to reconsidered, such as if further prospective work is done, considering using telephone follow-up. There also needs to be consideration of taking into account the effect of the better seeing eye on quality of life.

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Finally, I would like to thank the ophthalmology research team at York Teaching Hospital, in particular Alison Grice-Holt and Elizabeth Johnston.

Author's Declarations

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Chapter 2

The data from this chapter formed a published manuscript (Gill*,*C, Lightfoot,T, Hewitt, C and Gale, R (2020) Demographic and Clinical Factors that Influence the Visual Response to Anti-Vascular Endothelial Growth Factor Therapy in Patients with Neovascular Age-Related Macular Degeneration: A Systematic Review, *Ophthalmology and Therapy,* 9, 725 - 737).

Chapter 3

I was the chief investigator for this study, with the data being purchased from and anonymised by a research grant from the data company Medisoft.

Chapter 4

As this prospective study was an NIHR Portfolio study the data collection was aided by the Research and Development department at York Teaching Hospital, and particularly members of the ophthalmology research team Alison Grice-Holt and Elizabeth Johnson.

1.0 Background

The objectives of this background chapter are:

- To discuss what nAMD is and why it is important in an ageing population
- To explain how there are variations in health outcomes in not only nAMD, but in non-eye related conditions
- To outline the aims, objectives, and structure of this thesis

1.1 Structure and content of thesis

This thesis contains five chapters, of which this background chapter is the first.

Chapter 2 presents a systematic review of journal articles and grey literature exploring clinical and demographic factors that affect the success of anti-VEGF therapy in patients with nAMD. The literature draws upon findings from included studies conducted after 2005, because this is when anti-VEGF therapy began to be used in nAMD. Then the results of the systematic search are presented, and findings from included papers synthesised.

Chapter 3 of the thesis builds upon the known factors established in Chapter 2, using a retrospective analysis of a large real-world dataset, from seven UK ophthalmology departments, with a mixture of district and teaching hospitals. The chapter will begin with a description of the dataset. The chapter then moves on to investigate further which factors can be identified as influencing visual outcome in patients with nAMD being treated with anti-VEGF therapy, particularly those that it was not possible to identify in Chapter 2, for example ethnicity and social deprivation.

In Chapter 4, the findings of the levels of variation identified in Chapter 3 informed the basis of a prospective cohort study, undertaken at York Teaching Hospital, York, UK. In the dataset analysed in Chapter 3, although levels of variation are established,

there were no data on if and how this is associated with patient reported quality of life. Changes in visual acuity over a twelve-month period are described, along with changes in reported quality of life using a generic quality of life tool (EQ-5D-5L) and a vision specific tool (NEI-VF-5Q). These outcomes are modelled on visual outcomes, accounting for relevant factors identified as significant factors in Chapters 2 and 3. Therefore, the chapter will attempt to understand the relationship between visual outcome and quality of life in this cohort of patients. ?25Q

Finally, in Chapter 5, the overall findings of the chapters in this thesis are drawn together to understand what this really means for patients with nAMD. It positions the findings within the wider literature. This section also describes the limitations of this thesis, and how the methodology could have been strengthened. Finally, future areas of research are outlined.

1.2 The aims of this thesis

The aims of this thesis are to:

- Determine which factors influence the effectiveness of anti-VEGF therapy for patients with nAMD.
- Investigate how much variation there is nationally in visual outcomes in patients with nAMD being treated with anti-VEGF therapy.
- Investigate if there is a relationship between visual outcomes and patient reported quality of life outcomes.

1.3 Classifications of eye conditions

There are a range of eye conditions that can affect people of all ages and are grouped into the following categories: cataracts (a condition of the eye that causes clouding of the lenses), conditions of the eye socket or tear system (such as tear drainage disorders), front of the eye conditions (such as weakness in the structure of the cornea leading to pressure in the eyeball, which causes a condition called keratoconus), glaucoma (a condition where the optic nerve is damaged, which can lead to visual loss), retinal and macular conditions (such as diabetic retinopathy or macular degeneration), and visual disturbances and irregular eye movements (such as double vision) (NICE, 2019). The cause of these eye conditions could be trauma or injury related, or congenital (where a health condition is present from birth), or related to other health conditions such as diabetes, or age-related. Age-related macular degeneration (AMD) comes under the retinal and macular grouping of eye conditions (Solomon *et al.,* 2014). Figure 1 below shows that AMD fits into this category with some

retinal and macular conditions.

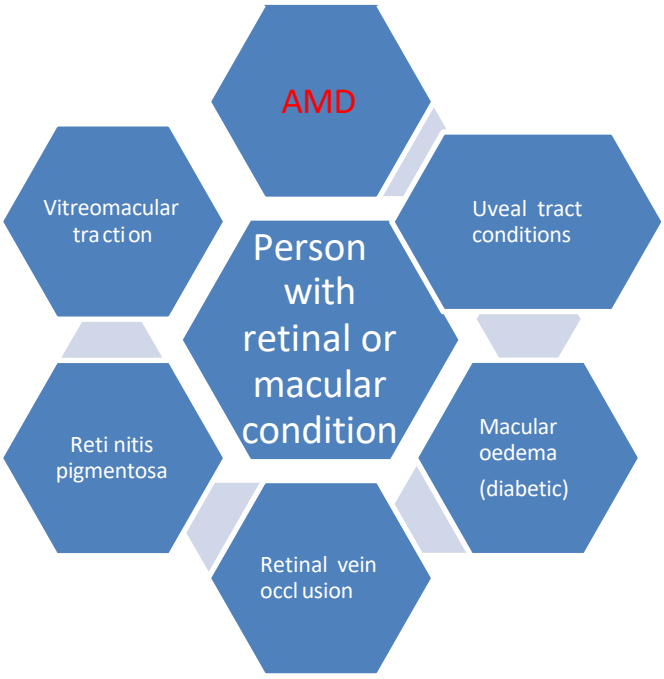
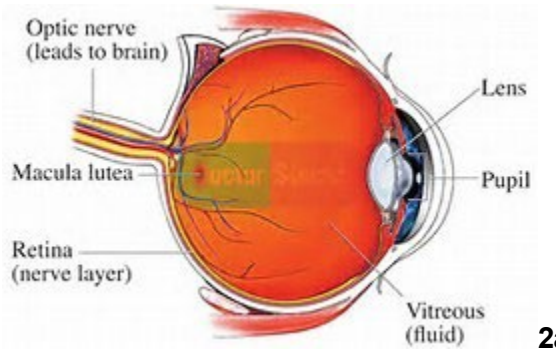


Figure 1: Example of retinal and Macular Conditions

1.4 Pathogenesis of AMD

AMD affects older adults of age 50 years and above, and the condition accounts for approximately half of all vision impairment or blind registrations in the developed world (Chakravarthy, 2010; Jager, 2008; Owen *et al.,* 2003 and Watkinson, 2010). It is caused by changes in the macula which is the central area of the retina (see Figures 2a and 2b). People have naturally occurring antioxidants that manage oxidative damage to photoreceptors (a degradation of the visual cells in the eye due to the environment lived in); as people age, levels of antioxidants, such as glutathione, decrease (Watkinson, 2010; Zafrilla *et al.,* 2015). Inflammation also plays a part in the development of nAMD, as do genetic risk factors that show mutations in the complement cascade (the part of the immune system that enhances the ability of immune cells to clear microbes and damaged cells, promote inflammation and attack the membrane of pathogens (Sergeive *et al.,* 2018). These changes lead to the formation of sub-retinal deposits called drusen. The more deposits that occur the worse the prognosis and highlights progression of the disease.



2a 2b

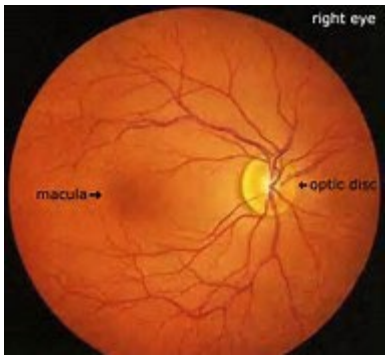
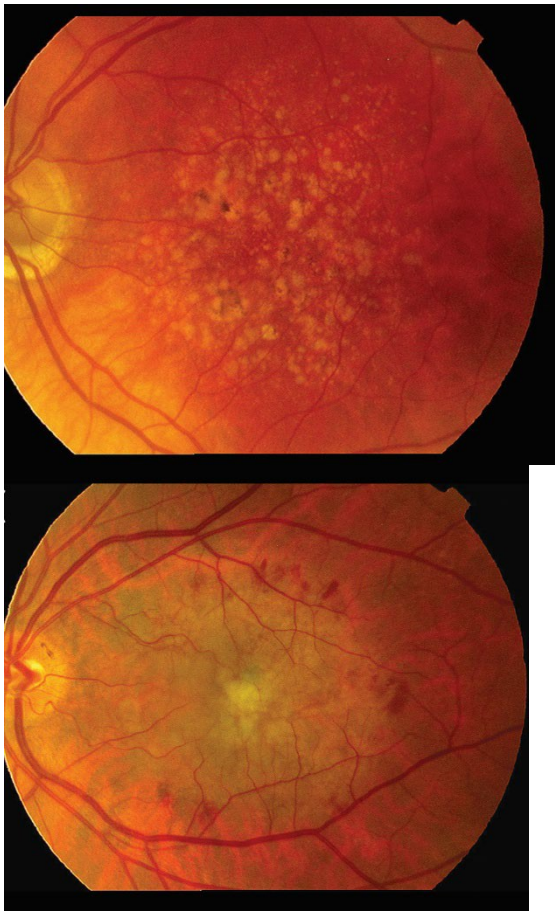


Figure 2a: Anatomy of the eye showing the location of the macula (taken from doctorstock.photoshelter.com). Figure 2b: Fundus photograph of the eye showing the macula (taken from forbestvision.com).

The presence of drusen is normally the first clinical sign of AMD (Jager, 2008) (See figures 3a and 3b). Alongside the formation of drusen, progressive diffuse thickening of Bruch's membrane (a layer of the retina that plays an important compartmental role in the growth of vessels on the retina) can occur. Bruch's membrane is a non-cellular part of the choroid (the vascular layer of the retina). The thickening of Bruch's membrane leads to a reduced ability for oxygen to diffuse through to the retinal pigment epithelium (RPE) (a layer of dark tissue that absorbs excess light) and photoreceptors (unique cells in the retina that are responsible for converting light into signals that are sent to the brain) and leads to hypoxia (lack of oxygen). In turn, this gives rise to the release of growth factors and the subsequent development of new choroidal blood vessels (Jager, 2008 and Watkinson, 2010). A break in Bruch's membrane leads to choroidal neovascularisation (CNV) forming under the retina, which leads to the leakage from these vessels of blood, or serous fluid (a clear, watery fluid) and causes distortion and reduced acuity of central vision (Watkinson, 2010).



3a **3b**

Figure 3a: Fundus photograph of a left eye showing the yellow lesions of drusen, and hyperpigmentation centred on the macula. Figure 3b: Fundus photograph of an eye showing large areas of drusen around the macula, but with accompanying haemorrhage at the borders of the lesion. (Both images taken from Chakravarthy *et al.*, 2010).

1.5 Age-related macular degeneration

AMD can be dry and wet (or neovascular). Dry AMD accounts for approximately 85% of total AMD cases, and is characterised by a mild to moderate loss of central vision, with retention of peripheral vision (Chakravarthy *et al.*, 2010; Jager, 2008; Watkinson, 2010). In dry AMD onset is insidious and gradual, with loss of vision occurring over a

period of months to years. There is currently no NHS funded licensed treatment for dry AMD, although research into this continues. Genetics plays a crucial role in whether dry AMD progresses to advanced or wet AMD, as do lifestyle choices such as smoking, obesity, lack of exercise, and diet lacking fruit and green vegetables.

Although wet, or nAMD only accounts for 10-15% of total AMD cases, it causes 80% of cases of blindness (Emsfors *et al.,*2017; Jager, 2 Rastion *et al.,* 2020; Watkinson, 2010; Zafrilla *et al.,* 2013;). nAMD differs clinically from the dry form by the presence of RPE detachment, leakage from choroid blood vessels due to increased levels of VEGF. This leads to scar or glial tissue and macular hard exudates (Beatty *et al.,* 2000). nAMD is also characterized by an acute onset and can develop in a matter of days to weeks.

Risk factors for nAMD include advanced age, white race, being a current or past smoker, genetic factors, obesity, exposure to sunlight and high intake of vegetable fat (Chakravarthy *et al.*, 2010; Jager, 2008). Although there is good evidence for age, white race, smoking, genetic factors and obesity being risk factors for progression to wet AMD, there is less robust evidence for exposure to sunlight and high intake of vegetable fat. In 2010, Chakravarthy *et al.* conducted a systematic review and meta- analysis looking at the strength of association for various risk factors for the development of nAMD (Arai *et al.,* 2019). The risk factors that had the strongest association with nAMD included increasing age, current cigarette smoking, previous cataract surgery, and family history of AMD (Chakravarthy *et al.,* 2010). A large systematic review and meta-analysis of risk factors for nAMD has not been conducted since then.

Many patients with nAMD in one eye go on to develop nAMD in both eyes (known as bilateral nAMD). In a multicentre, national nAMD database study conducted in the UK, 14% of patients per year were found to develop second eye involvement (Zarranz- Ventura *et al.*, 2014). There are also rarer occasions when a patient will be diagnosed with nAMD in both eyes at the same time (Chakravarthy *et al.,* 2010). In a study of an elderly white UK sample of patients, 21.9% were found to have bilateral nAMD (Wilde *et al.,* 2017). Risk factors for bilateral nAMD include genetic components (as in naturally occurring DNA influences) and severity of nAMD in the first eye.

1.6 Epidemiology

1.6.1 Global prevalence of nAMD

The World Health Organisation (WHO) (2017) ranks AMD as the third global cause of blindness after cataract and glaucoma. nAMD is not only a leading cause of blindness in developing countries, it is also a significant burden. Large scale epidemiological studies highlight that nAMD prevalence is increasing in developing countries such as India, as a consequence of a rise in life expectancy (Chakravarthy *et al.,* 2010; Ricci *et al.,* 2020).

1.6.2 Prevalence of nAMD in developed countries

It is known that nAMD is one of the leading causes of blind registrations in the developed world (Villeges *et al.,* 2017). However, Owen *et al.,* (2003) argues that there have been reports of substantial under-registration of blindness and its causes. The introduction of standardised photographic documentation and grading systems has allowed pooling of prevalence data from population-based epidemiological studies (La Cour *et al.,* 2002). In 2003, Owen *et al.* pooled data from 31 populations similar to the UK (n=>500,000) and found the estimated prevalence of AMD (both wet and dry) to be 4.8% in the over 65s, and 12.2% in those 80 or above (Owen *et al.,* 2003). However, a more recent UK study population from 2007-2009 found the prevalence of nAMD to be 1.2 to 6.3%, which equates to 39,800 people developing nAMD each year and 663 cases per million per year (NICE, 2018). This is quite a wide prevalence rate, which may be due to different study populations and methodologies. and perhaps the long period of time these studies cover (from 2003 – 2018).

The prevalence of nAMD increases exponentially with age (Cruess *et al.,* 2008; Royal College of Ophthalmologists, 2022; Owen *et al.,* 2003; Papadopolous, 2020). However, nAMD is more prevalent in Caucasians, and in black people nAMD does not appear to increase exponentially with age (La Cour *et al.,* 2002).

Increasing presence of an ageing population in developed countries could increase the burden of visual disability due to nAMD (Cruess *et al.,* 2008; Royal College of Ophthalmologists, 2013; Owen *et al*., 2003). Owen *et al.* (2003) predicted that the burden of nAMD will increase by a third between 2010 and 2020, which did occur.

1.7 Costs of nAMD

Global estimates of the cost of AMD are $343 billion dollars, including $255 billion dollars in direct healthcare costs (WHO, 2017). In the UK, nAMD represents a significant use of NHS resources.

Ophthalmology accounts for 10% of all outpatient attendances in the NHS, with management of AMD constituting 15% of all ophthalmology appointments (Royal College of Ophthalmologists, 2013).

Cruess *et al.* (2008) estimated the annual societal costs of patients with bilateral nAMD treated in the UK; this ranged from £236 million to £576. This includes direct treatment costs, and costs resulting from medical treatment for falls, and costs of assistance with daily living. nAMD has a profound effect on quality of life, life expectancy and environmental risks, and the literature suggests that the socioeconomic effects of nAMD need further investigation (Schmidt-Erfurth *et al.,* 2014).

1.8 Symptoms and diagnosis of nAMD

Symptoms of nAMD include blurred vision and visual disturbances of rapid onset, worsening of visual symptoms, and central dark spots (NICE, 2018). Patients with suspected nAMD should have an urgent referral made to a macula service within one working day and have their first treatment within two weeks (NICE, 2018). Most referrals are made by optometrists in community optician practices with a smaller number of patients referred by their GP. Once referred to a macular service, a diagnosis will be made by a macula specialist

ophthalmologist using a clinical examination, and detailed imaging of the eyes. The clinical examination will typically include vision measurement, clinical examination using a slit lamp and optical coherence tomography (OCT) investigation. An Amsler Grid is used for home monitoring, using a light to look at the retina of the eyes, and the use of an Amsler Chart (Faes *et al.,* 2014)(see Figure 4 below).

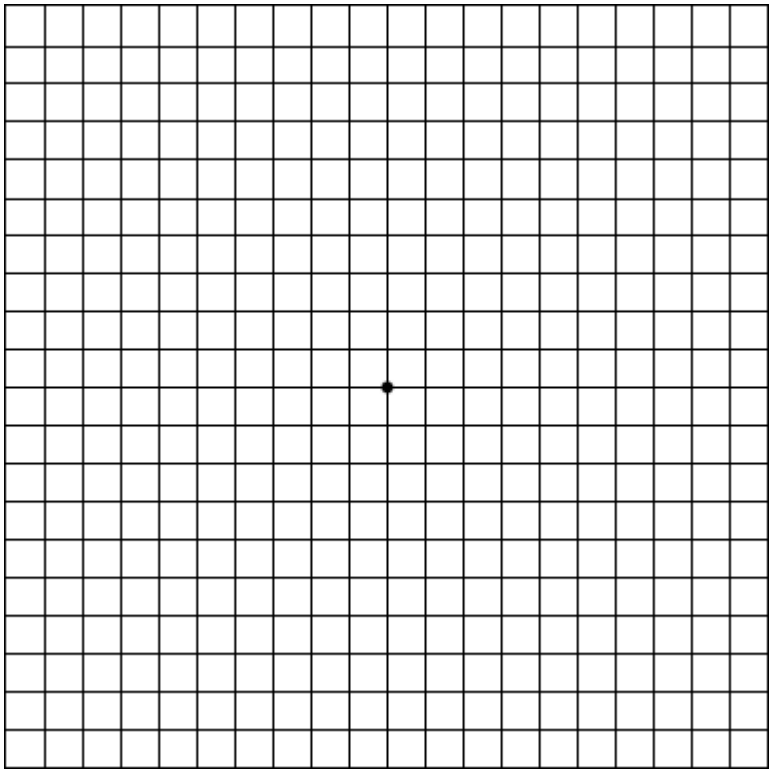


Figure 4: Amsler Chart (courtesy of allaboutvision.com)

The patient will be asked if any of the lines look distorted or wavy, whether there are any lines missing, or whether there are any boxes that are different sizes. If this is the case, then it may indicate the presence of macular disease. The patient will also have their visual acuity measured using one of three different visual charts. Snellen acuity, LogMar and Treatment Diabetic Retinopathy Score (ETDRS) letter score.

Snellen charts, named after a Dutch ophthalmologist, were a more traditional method of visual acuity measurement and use a fractional method of visual acuity testing. For example, 6/6 is considered to be normal visual acuity (NICE, 2018). Snellen scoring in the UK takes place at 6 meters. If a person has very poor visual acuity and can only read the top line of the chart, they would have a Snellen score of 6/60; this means that they could only see at 6 meters something that someone with normal vision could see at 60 meters. The problem with Snellen charts is that they do not have an equal number of letters on each line, which creates difficulty in standardized scoring (Tsui and Patel, 2020).

To solve this, the LogMar chart was introduced. It was originally used in research because of its high accuracy, but is now routinely used in clinical practice. LogMar charts have even numbers of letters on each line, and even spacing of LogMar lines of letters (NICE, 2018).

LogMar is presented as a decimal fraction of visual loss, with normal vision being LogMar 0.00, and poor vision would be 1.00 LogMar. There is no direct

correlation between Snellen and LogMar, but in order to enable a Snellen score to be converted to a more accurate LogMar score, a conversion table can be used (Daiber and Gnugnoli, 2022). There are LogMar 1 and LogMar 2. This represents different standardised versions of LogMar charts to prevent memorisation, with only one of the two LogMar charts used at each eye examination.

ETDRS letter score is the measurement of visual acuity using a logarhythmic style chart with similar principles to the LOGMAR chart called ETDRS (Wang *et al.,* 2021). This chart was traditionally just used in research, but is now used in clinical settings. Letter score is the number of letters on this chart that can be correctly read from specified distances. A higher number of letters represents a better visual acuity, and a lower number of letters a poorer visual acuity. The chart has 5 evenly spaced letters per row. The person begins reading each row of letters out until they reach a line where they cannot read a minimum of 3 letters. The patient then receives a score based on how many letters were identified. There are 3 different standardized versions of the ETDRS chart to avoid memorization Wang *et al.,* 2021).

Optical coherence tomography (OCT) is a non-invasive procedure that uses light waves to form an image of all the layers of the retina. Assessment of each of the layers of the retina help to make a diagnosis of nAMD (Chakravarthy *et al.,* 2010). Figure 5 below shows an OCT image of a normal retina.

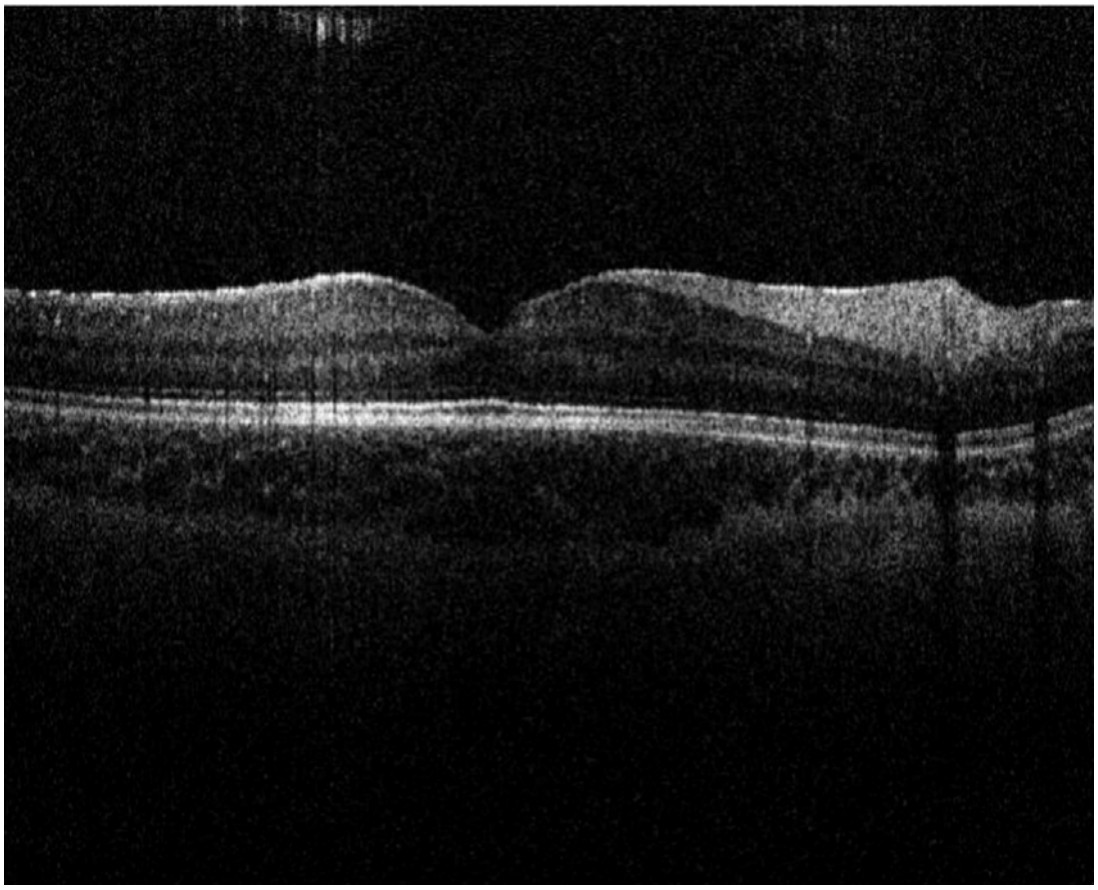


Figure 5: OCT image of a normal macular region (taken from https://www.researchgate.net/figure/Optical-coherence-tomography-OCT-of-the-right-eye-Normal-retinal-layers-are-observed_fig2_313287601)

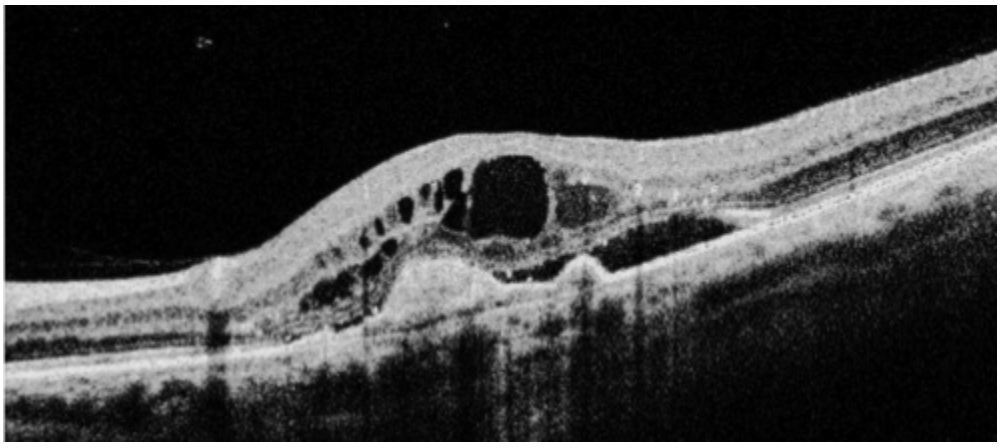


Figure 6: OCT image of a retina with nAMD, showing fluid within and beneath the retina (the black spaces) and therefore a greater retinal thickness (taken from https://www.researchgate.net/figure/OCT-images-of-the-retina-for-a- healthy-and-pathologic-human-eye-A-Image-of-the-retina_fig1_7668733)

If OCT imaging fails to provide a conclusive diagnosis of nAMD, fundus fluorescein angiography (FFA) is the standard reference test. This is an invasive procedure, that uses a dye inserted into the patient's vein, to detect neovascular tissue which will fill with the dye if present. If a confirmed diagnosis of nAMD is made, the patient should begin treatment as soon as possible, ideally within 14 days from the time of referral (NICE, 2018).

1.9 Treatment of nAMD

Historically, treatment for nAMD was largely social and lifestyle support, and the prescription of visual aids (Boyle *et al.,* 2014). When left untreated, almost 50% of patients with nAMD will lose at least three lines of vision on an ETDRS visual chart over a 2- year period (Pedrosa *et al.,* 2017). However, treatment and prognosis were revolutionised by the introduction of anti- VEGF (Ross *et al.,* 2013; Johnston *et al.,* 2017; Boyle *et al.,* 2018; Royal College of Ophthalmologists, 2013; Brown *et al.,* 2006; Rosenfeld, 2006). Anti-VEGF is a growth factor that stimulates vascular permeability and has a major role in the pathology of CNV (Boyle *et al.,* 2014). It is this neovascularisation that leads to visual loss. Anti-VEGF agents work by binding and inhibiting VEGF, therefore reducing CNV. They were originally used to treat cancer but were discovered to be effective in nAMD. The Royal College of Ophthalmologist's 2013 guidelines recognise anti-VEGF therapy as the recommended standard of care. Although anti-VEGF is not a curative treatment for nAMD, the aim of its use is to slow disease progression and maintain optimal vision for as long as possible (Boyle *et al.,* 2018; Yang *et al.,* 2016).

Ranibizumab and Aflibercept are the two most used licensed treatments in the UK, and intravitreal injections are given directly into the vitreous (the gel-like fluid that fills the eye) under drops of local anaesthetic. Aflibercept is usually administered, with a three-month loading phase treatment (where a patient with newly-diagnosed nAMD is given an initial once-monthly dose of anti-VEGF for three months) (Johnston et al., 2017; NICE, 2018; Royal College of Ophthalmologists, 2013). During the

loading phase, injections are given on a four-weekly basis. In order to prevent ocular infection, administration of anti-VEGF follows peri-orbital skin cleansing, ocular surface sterilisation, orbital draping, and insertion of a sterile lid speculum.

MARINA and ANCHOR were the landmark RCTs that defined the gold standard for visual acuity (VA) that can be achieved for selected patient populations with monthly injections of Ranibizumab for 24 months (Ross *et al.,* 2013). For example, the MARINA study demonstrated that in patients treated with a 0.5mg dose of Ranibizumab, at 12 months there was a mean improvement of +7.2 letters on ETDRS; at 24 months this mean improvement was +6.6 letters (Rosenfeld *et al.,* 2006). In the ANCHOR trial, 34 to 41% of patients being treated with ranibizumab had gained 15 or more letters from baseline at 2 years, compared to only 6.3% of those treated with laser therapy (Brown *et al.,* 2009). Given that Pedrosa *et al.* (2017) identify that almost 50% of nAMD patients will lose at least three lines of vision over two years without treatment, in contrast they assert that 80% of patients undergoing Ranibizumab therapy will avoid visual loss in that same period. However, this was not a double blind trial. But the size of this trial does make it generalizable. The pivotal clinical trials in anti-VEGF therapy for nAMD also consistently demonstrate the safety of its use (Boyle *et al.,* 2014). Therefore, the overall effectiveness of anti-VEGF therapy is clear.

However, identifying the most effective treatment pattern for nAMD still remains a challenge, with the ideal being to keep the number of intravitreal injections to a minimum, without sacrificing VA (Johnston *et al.,* 2017). Ross *et al.* (2013) highlights how the monthly administration regimes place a considerable burden on patients, ophthalmology services and healthcare budgets. There have been some studies that have investigated less frequent dosing regimens with treatment as required (*pro re nata or prn*) with monthly attendance. For example, the prONTO study, a small case series, demonstrated comparable outcomes to ANCHOR and MARINA, with a mean of 5.5 injections in year one, and 4.4 injections in year two (Lalwani *et al.,* 2009). It is important to investigate treatment burden, because as the prevalence of nAMD rises with an ageing population, so will the number of people who require treatment. Less frequent dosing regimens are an option to reduce treatment burden. The VIEW study showed that 2-monthly fixed dosing with Aflibercept provided similar outcomes with less burden, and the TREX study showed similar outcomes with less burden with a Treat and Extend regimen (Heier *et al,.*2012; Wycoff *et al.,*2015). Boyle *et al.* (2018) found that although at time of diagnosis most patients consent to and agree to being compliant with the treatment regimen, a significant proportion of these patients are

lost to follow-up or do not adhere strictly to the regime at the end of year one. Hence, reducing treatment frequency may improve compliance with the treatment regimen.

Overall, patients who receive regular anti-VEGF therapy for nAMD can expect to slow the progression of the disease overall, and are likely to retain their sight, even though visual acuity tends to worsen over time. However, some patients will still lose their sight. (Airody *et al.*, (2015)).

1.10 Variation in nAMD visual outcomes

There are certain epidemiological, functional and anatomical/morphological factors that are significantly associated with visual outcome. These factors are age of patient, lesion characteristics, duration of disease and baseline VA; baseline VA had the strongest association to visual outcome (Amoaku *et al.,* 2015; Liew *et al.,* 2016; Tsilimbaris *et al.,* 2016). Increased age, increased lesion size, longer duration of disease, and poorer baseline VA were associated significantly with poorer visual outcomes (2016Amoaku *et al.,* 2015; Liew *et al.,* 2016; Tsilimbaris *et al.*). However, although these factors go some way in explaining variations in visual outcomes, they do not explain this fully.

Despite anti-VEGF therapy showing significant improvements in visual prognosis overall, there are variations in the visual outcomes of patients with nAMD who are treated with anti-VEGF therapy. Previously there was no consensus on how to classify optimal response to treatment, or lack of it; in 2015 Amoaku *et al.* developed the classifications of good response, poor response, and non-response. The classification criteria they developed are given below in Table 1.

Classification	Criteria
Good Response	• Improvement of >5 letters (subject to ceiling effect) • Resolution of intraretinal fluid (IRF) and subretinal fluid (SRF)
Poor Response	• Change in VA of 0-4 letters • <25% reduction from baseline in central retinal thickness (CRT), IRF and SRF
Non-Response	• Loss of >5 letters compared with baseline or best corrected visual acuity (BCVA) • Increase in IRF, SRF and/or CRT, increase in haemorrhage

Table 1: Classifications of Visual Response to Treatment (Amoaku *et al.*, 2015)

IRF= Intraretinal Fluid, SRF= Subretinal Fluid, CRT= Central Retinal Fluid, BCVA= Best Corrected Visual Acuity

Liew *et al.* (2016) identified that while there was significant data for variation in nAMD outcomes between different countries, both developed and developing, there is little known about intra-country and intra-regional variations in outcomes for nAMD. Although the overall effectiveness of anti-VEGF treatment is clear, there is individual variability in clinical response and therefore visual outcomes (Pedrosa *et al.,* 2017). The pivotal phase III clinical trials of anti-VEGF agents demonstrate this individual variability amongst their sample of participants. Although the ANCHOR and MARINA trials overall showed increases in visual acuity over their two-year study periods, pooled data from both trials contained a small subset of participants (10%) who still lost at least three lines of vision despite adequate levels of treatment (Pedrosa *et al.,*2017; Brown *et al.,* 2006; Rosenfeld *et al.,* 2006; Tsilimbaris *et al.,* 2016). Development of atrophy, that is unwanted loss of photoreceptors and the supporting retinal pigment epithelial layer, is likely to play a part in this.

Variation was also demonstrated amongst those who were responsive to treatment, with some of the more responsive participants gaining an impressive three lines of visual acuity overall (Brown *et al.,* 2006; Pedrosa *et al.,* 2017; Rosenfeld *et al.,* 2011). At month 24 in the ANCHOR and MARINA trials, 30% of participants achieved a 15-

letter improvement from baseline (Brown *et al.,* 2006; Rosenfeld *et al.,* 2011; Tsilimbaris *et al.,* 2016). Observational studies and systematic reviews have demonstrated similar variations in visual outcomes (Liew *et al.,* 2016; Pedrosa *et al.,* 2017; Tsilimbaris *et al.,* 2016). However, randomised controlled trials have the advantage of much more closely controlled environments and treatment patterns and attendances that is simply not possible to replicate in observational studies. It could be argued that real world observational studies more closely reflect unwarranted variations.

Some importance has been attached to being able to predict more accurately visual outcomes in nAMD. The reasons for this include the possibility that it would allow ophthalmologists and their patients to adjust their expectations for visual outcomes. It may help to optimise treatment by identifying patients who require more frequent anti- VEGF injections, thereby avoiding under or over treatment. Finally, it may further expand knowledge of the pathogenesis of nAMD that could lead to the development of alternative treatment strategies (Pedrosa et al., 2017; Tsilimbaris et al., 2016).

1.11 Unwarranted variation across the NHS

The variation in visual and financial outcomes of patients with nAMD treated with anti- VEGF therapy is part of a much bigger picture of unwarranted variation throughout the NHS. For several decades health service researchers have documented extensive variation in the delivery of healthcare in the NHS, and the last 30 years in particular have witnessed multiple efforts to tackle unwarranted variation (Wennberg, 2011; Arie, 2017).

There are wide-ranging examples of variations throughout the NHS; the average cost of an inpatient treatment is £3,500, but there is 20% variation in this, with the least expensive trusts costing £3,150 and the most expensive trusts spending £3,850; the average price paid for hip prosthesis varies from £788 to £1,590, with the trusts who are spending the most also buying the most (Department of Health (DoH), 2015). The average length of stay for appendicectomy is just over 3.5 days, with some trusts discharging nearly half of patients after just two days; if all trusts matched this performance, not only could 30,000 bed days be saved, but also the costly need to outsource operations to private providers could be reduced (Arie, 2017).

Such information on variation within the NHS raises important questions about efficiency and effectiveness (Wennberg, 2011). The examples of unwarranted

variation given above represent an opportunity for better use of already strained NHS resources, by trusts heeding the examples of their more efficiently performing counterparts. In response to this, in 2015 the DoH commissioned the Lord Carter report on operational productivity and performance in English NHS acute hospitals, focusing on unwarranted variations. As the NHS was expected to deliver efficiencies of 2 to 3% per year, the Carter report aimed to look at efficiencies in non-specialist acute hospitals, as these account for half of the healthcare budget per year (DoH, 2016). It looked at the key resource areas of clinical staff, pharmacy and medicines, diagnostics and imaging, procurement, back-office functions, and estates and facilities (DoH, 2016). The report concluded that unwarranted variation is worth £5bn in terms of efficiency, and accounts for a contribution of nearly 10% of the money spent by acute trusts (DoH, 2015). However, there are also variations in health outcomes.

The findings of the report give further importance to the need to identify and understand levels of unwarranted variation in the visual outcomes of patients with nAMD being treated with anti-VEGF therapy.

2.0 Demographic and clinical factors that influence the visual response to anti-vascular endothelial growth factor therapy in patients with neovascular age related macular degeneration: A systematic review.

As highlighted in the previous Chapter, effective treatment with anti-VEGF agents is key to preventing significant visual loss in patients with nAMD (Chakravarthy *et al.* 2010 and Cruess *et al*. 2008). However, although clinical trials have demonstrated this effectiveness, this often is not matched in real- world data. (Chakravarthy *et al.,* 2010; Gale *et al.,* 2016). This is due to the fact that clinical practice often fails to replicate the treatment patterns of clinical trials. Hence, this chapter will seek to identify clinical and demographic factors that could have an impact on the success of treatment for nAMD.

2.1 Introduction

Untreated nAMD leads to severe visual loss in most patients over a 2-year period Anti-VEGF treatment given regularly stabilises vision in around 95% of those with nAMD (NICE,2018). It has been shown that over a four-year period of treatment with Ranibizumab, cumulative incidence of new blind registrations was 5.1% in year 1, 8.6% in year 2, 12% in year 3 and 15.6% in year 4, demonstrating significant reductions in blind registrations once treatment is initiated (Tufail *et al.*,2014). However, there is variability in both individual and patient group clinical response and consequently visual outcomes (DoH, 2015). Real-world clinical effectiveness has broadly not managed to reproduce this efficacy (Liew et al.,2016 and NICE, 2018;). Genetic factors affecting visual outcomes have already been well reported on and established in the literature. This has found that genetic factors play a strong role in determining both the risk of developing nAMD, and the risk of severe disease (Abedi et al., 2012; Coleman et al., 2008; Moshfeghi and Blumenkrank, 2007 and Sergeive et al., 2018). For example, it has been found that genes associated with nAMD are those that control the complement system (the part of the immune system that enhances the ability of immune cells to clear microbes and damaged cells, promote inflammation and attack the membrane of pathogens (Sergeive *et al.,* 2018)). There are also certain genes that are associated with poorer visual outcome when a patient is treated with certain anti-VEGF treatments, such as bevacizumab and ranibizumab, and the use of genetic information can help with more individualized treatment regimens (Abedi *et al.,* 2012).

The pivotal phase III clinical trials of anti-VEGF agents demonstrate this individual variability in outcome amongst their sample of participants (Liew et al., 2016 and NICE, 2015). This trial found that of 140 patients receiving 0.5mg of ranibizumab, 96.4% had

lost fewer than 15 ETDRS letters and visual acuity improved by 15 letters or more in 40.3% at 12 months. It has been questioned whether there are demographic and clinical factors that could affect this variation in clinical response. (Bloch *et al.,* 2013*).*

The aim of this review is to identify whether there is any evidence of variation in the effectiveness of anti-VEGF therapy for nAMD based on demographic and clinical factors.

2.2 Methods

The methodology of this systematic review follows recommendations by the PRISMA guidelines (a minimum set of reporting standards for systematic reviews). The protocol for this systematic is registered with PROSPERO (the international prospective register of systematic reviews) (registration number: CRD42018094191; https://www.crd.york.ac.uk/PROSPERO/. As this was a review of published literature, there was no requirement to seek ethical approval.

2.2.1 Searches

The major electronic databases including MEDLINE, EMBASE, Web of Science, CINAHL and the Cochrane Library, were searched for relevant published literature. Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including the National Research Register, Current Controlled Clinical Trials, ClinicalTrials.gov and the International Standard Randomised Clinical Trials Number (ISRCTN) registry. Studies dating from 2006 to the present will be included in the search strategy, because anti-VEGF began to be used for nAMD in clinical practice from 2006. Bibliographies of previous systematic reviews and retrieved articles were also examined. A copy of the search strategy can be found in Appendix 1. The search took place between the 10th of January and 25th March 2018.

2.2.2 Types of study to be included

Secondary analysis of randomised controlled trials, prospective cohort studies, retrospective cohort studies.

2.2.3 Condition or domain being studied

Neovascular age-related macular degeneration (nAMD). Clinical and demographic factors

affecting the effectiveness of treatment.

2.2.4 Participants/population

Inclusion: Patients with nAMD being treated with anti-VEGF therapy.

Exclusion: Patients with nAMD not being treated with anti-VEGF therapy, patients with non exudative AMD.

Intervention(s), exposure(s)

There has been a significant amount of observed variation in visual outcomes in patients with nAMD being treated with anti-VEGF therapy. There are certain epidemiological, functional and anatomical/morphological factors that are significantly associated with visual outcome. These include smoking history, BMI, baseline visual acuity, and baseline lesion size.

2.2.5 Comparator(s)/control

No control. The aim of the review is to capture all significant clinical and demographic factors that influence visual outcome.

2.2.6 Context

UK hospitals and comparative settings.

2.2.7 Main outcome(s)

• Visual acuity (measured using the Early Treatment Diabetic Retinopathy Study chart)

• Visual response classification

• Central retinal thickness

• Intraretinal fluid

• Subretinal fluid

Additional outcome(s)

None.

2.2.8 Data extraction (selection and coding)

Data relating to study design, methods and findings around clinical and demographic factors influencing anti-VEGF therapy were be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted using a standardized data extraction form. If required and if time permits, attempts will be made to contact authors for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all relevant other publications listed.

2.2.9 Risk of bias (quality) assessment

The methodological quality of the included studies will be assessed according to appropriate criteria based on the study design. As the included studies were secondary analyses, retrospective and cohort studies, The Newcastle Ottawa Scale to assess quality. For each domain in the tool, we will describe the procedures undertaken for each study, including verbatim quotes. A judgement as to the possible risk of bias in each of the six domains will be made from the extracted information, rated as ‘high risk’ or ‘low risk’. If there is insufficient detail reported in the study judge the risk of bias as ‘unclear’ and the original study investigators will be contacted for more information. The quality of the individual studies will be assessed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The possible effects of study quality on the effectiveness data and review findings will be discussed.

2.2.10 Strategy for data synthesis

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. It is intended that a meta-analysis will be undertaken. However, a finding may be that this is not possible because it is anticipated that there will be substantial heterogeneity in the studies included in the review. If estimates or mean differences for continuous data with confidence intervals are presented, the review will look to pool them using generic inverse variance if this is possible. Random effects (RE) models will be used in the analysis, and will be presented as forest plots.

2.2.11 Analysis of subgroups or subsets

If the necessary data are available, a sub-group analysis for different anti-VEGF agents. The review will look to pool the data on each anti-VEGF agent if possible using generic inverse variance.

2.2.12 Eligibility Criteria

Table 2 gives the inclusion/exclusion criteria for the search.

Population	Adult patients being treated for nAMD with anti-VEGF
Factors under Investigation	Presence or absence of demographic or clinical factors
Settings	Comparable settings to UK hospitals, such as those in developed countries
Outcomes	Visual response classification, visual acuity (VA), best corrected visual acuity (BCVA),central retinal thickness (CRT), intraretinal fluid (IRF), subretinal fluid (SRF).

Table 2: Inclusion Criteria

For the purposes of this review, the term demographic factors refer to individual patient characteristics such as age and ethnicity. The term clinical factors refer to clinical features of the disease at diagnosis such as lesion size, and features of patients' treatment in nAMD clinic, such as number of injections. Similar definitions have been used of demographic and clinical factors in a large retrospective study of UK intra-centre variation (Liew *et al.,* 2016). It focused on settings comparable to UK hospitals for the sake of comparability, as it would be more difficult to compare treatment patterns and outcomes in those in some developing countries, for example, as treatment for nAMD may not be as widely established or available at all. It was decided to only include papers from 2006 onwards because anti-VEGF treatment was not being widely used to treat nAMD until then.

2.2.13 Study Selection

The citations identified by the search strategy were assessed for inclusion in two stages, and by two reviewers independently. Stage 1 involved two reviewers independently screening all relevant titles and abstracts identified via electronic searching to identify potentially relevant studies for inclusion in the review. Stage 2 focused on the independent assessment of the full-text copies of those studies identified in phase 1 by two reviewers. Any disagreements between reviewers were resolved by discussion at each stage.

2.2.14 Risk of bias in individual studies

The methodological quality of the included studies was assessed using the Newcastle Ottawa Scale. The Newcastle Ottawa Scale is a widely used tool to assess the quality of non-randomised observational studies (Lo *et al.,* 2014). A copy of this can be found in Appendix Two. A judgement as to the possible risk of bias in each of the six domains was made from the extracted information, rated as 'high risk' or 'low risk'. Where there was insufficient detail reported in the study the risk of bias was recorded as 'unclear'. The quality of the individual studies was assessed by one reviewer, and a sample of quality assessments independently checked by a second. Disagreements were resolved through consensus.

2.3 Results

Of the 4,835 citations identified from the search, 2,604 titles and abstracts were screened (stage 1) with 28 included in stage 2 screening. Three additional papers were identified from hand searching and 1 paper was unavailable. Overall, there were
27 papers included in this review; 2 were prospective cohort studies (El-Molayess *et al.,* 2013 and Van Asten *et al.,* 2014), 16 were retrospective cohort studies (Abedi *et al.,* 2013; Airody *et al.,* 2015; Bloch *et al.,* 2013; Calvo *et al.,* 2015; Chatzaralli *et al.,* 2016; Chaprek *et al.,* 2015; Essex *et al.,* 2016; Gupta *et al.,* 2011; Guber *et al.,* 2014;Jonas *et al.,* (2011); Korb *et al.,* 2013; Ozkaya *et al.,* 2014; Razi *et al.,* 2016; Shona *et al.,* (2011); Singh *et al.,* 2011 and Subhi and Sorenson, 2017)and 7 were secondary analyses of trial data (Brown *et al.,* 2013; Fang *et al.,* 2013; Gale *et al.,* 2016; Holz *et al.,* 2016; Regillo *et al.,* 2015; Rosenfeld *et al.,* 2011 and Ying *et al.,* 2015).
The included studies represented >24,500 patients in total. The characteristics and outcomes assessed in each study are presented in Table 3.

Overall, the methodological quality of the included studies was very good. All the studies were quality assessed using the Newcastle Ottawa Scale and were rated as being at low-risk of bias. All the studies scored at least 5 stars out of a possible 7, with most of the studies achieving 6 stars. One study only scored 5 stars because its follow-up procedures were unclear. All of the other studies scored 6 stars as they did not have a comparison arm. The high quality of the studies included in this review informed the narrative synthesis of the findings.

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
Abedi *et al.*, (2013)	2006-2010	Australia	Single centre (Royal Victoria Eye and Ear Hospital).	Retrospective cohort study	224 consecutive treatment naïve patients
Airody *et al.*, (2015)	2007-2013	UK	Single centre (York Teaching Hospital).	Retrospective cohort study	68 patients with nAMD who have completed 5 years of treatment with Ranibizumab
Bloch *et al.*, (2013)	1st January – 1st July 2007	Denmark	Single centre (Glostrup Hospital).	Retrospective review	279 patients who met the eligibility criteria of MARINA and ANCHOR studies.
Brown *et al.*, (2013)	September 2004 – March 2007	US	Multicentre	Secondary analysis of PIER study (Ranibizumab treated sub-groups)	121 PIER study participants

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
Calvo *et al.,* (2015)	1st October 2008 – 1st October 2012	Spain	Single centre (Miguel Servet University Hospital)	Observational, longitudinal, retrospective study	51 patients (51 eyes)
Chae *et al.,* (2015)	January 2006 – January 2013	Australia	Vitreous Retina Macula Consultants of New York (2 private practices).	Retrospective cohort study	138 patients (154 eyes) fit the inclusion criteria at 2 years, 106 patients (113 eyes) at 3 years, and 72 patients (74 eyes) at 4 years.
Chatzaralli *et al.,* (2016)	1st November 2013 – 30th September 2014	UK	Moorfields Eye Hospital	Retrospective cohort study	767 patients (535 eyes) of patients who had insufficient response to ranibizumab and were switched to aflibercept.

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
Chabblani *et al*., (2013)	April 2008 – December 2009	US	Single centre	Retrospective study	47 patients (50 eyes)
Chaprek *et al*., (2015)	September 2008 – June 2013	Czech Republic	Multi-centre (9 tertiary referral centres).	Retrospective database study	841 eyes with active CNV, and 312 eyes with inactive CNV.
El-Mollayess *et al.,* (2013)	September 2009 – April 2010	Beirut	Multi-centre (2 medical centres).	Prospective cohort study	90 patients: 30 in each group (group 1 >70 letters, group 2 70-61 letters, and group 3 60 to 51 letters).
Essex *et al.,* (2016)	2006 – 2014	Australia	Multi-centre	Retrospective database study	2096 patients (2096 eyes)
Fang *et al*., (2013)	January 2008 – January 2010	China	Multi-centre	Secondary analysis of data from NATTB trial	144 participants

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
Gupta *et al*., (2011)	2008	UK	Single centre (King's College Hospital)	Retrospective chart review	78 participants in total (47 in Loading Dose (LD) group and 31 in PRN group).
Gale *et al.,* (2016)	Unknown	UK	Multi-centre (Data from HARBOR, MARINA, ANCHOR and CATT).	Secondary analysis of trial data	1.631 subjects
Guber *et al*., (2014)	Unknown	Switzerland	Multi-centre (data from EYESWIDE database).	Retrospective review	210 eyes (182 patients)
Holz *et al*., (2016)	January 2000 – August 2009	Canada, France, Germany, Ireland, Italy, the Netherlands, the United	Multi-centre	Secondary analysis of study data	2227 participants

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
		Kingdom, and Venezuela.			
Jonas *et al*., (2011)	Unknown	Germany	Single centre.	Retrospective cohort study	48 patients (96 eyes)
Korb *et al.,* (2013)	Unknown	Germany	Single centre (Department of Ophthalmology, University Medical Centre of Johannes Gutenberg-University of Mainz, Germany.)	Retrospective review	165 eyes (165 patients)
Ozkaya *et al*., (2014)	January 2010 – January 2011	Turkey	Single centre (Beyoglu Eye Hospital.	Retrospective review	96 eyes (96 patients)

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
Razi *et al.,* (2016)	Unknown	UK	Single centre (Northampton General Hospital).	Retrospective review	70 patients (76 eyes)
Regillo *et al.,* (2015)	Unknown	US	Multi-centre.	Secondary analysis of HARBOR study data	500
Rosenfeld *et al.,* (2011)	Unknown	US	Multi-centre	Secondary analysis of MARINA and ANCHOR trials	757 participants
Rush *et al*., (2014)	January 2009	US	Single centre	Retrospective cohort study	230 eyes
Shona *et al.,* (2011)	Unknown	UK	Single centre (King's College Hospital).	Retrospective chart review	87 participants total (27 poor VA (24-34 letters), 33 intermediate VA (35-54), 27 with good VA (≥55)

Study	Year of Study	Country	Study Setting	Type of Study	Number of Participants
Singh *et al*., (2011)	Unknown	US	Cole Eye Institute	Retrospective analysis	73 eyes
Subhi and Sorenson (2017)	2009 – 2015	Denmark	Single centre (Department of Ophthalmology at Zealand University Hospital).	Retrospective chart review	20 patients age ≥90
Van Asten *et al.,* (2014)	June 2008 – June 2010	The Netherlands, Germany and Canada.	Multi-centre.	Prospective observational cohort study	391 patients
Ying *et al.,* (2015)	Unknown	US	Multi-centre (43 clinical centres).	Secondary analysis of CATT trial	1185 patients

Table 3: Study characteristics and outcomes

Overall, the included studies were observational cohort studies, retrospective studies or secondary analyses of trial data. Figure 7 gives a flow diagram of the inclusion process.

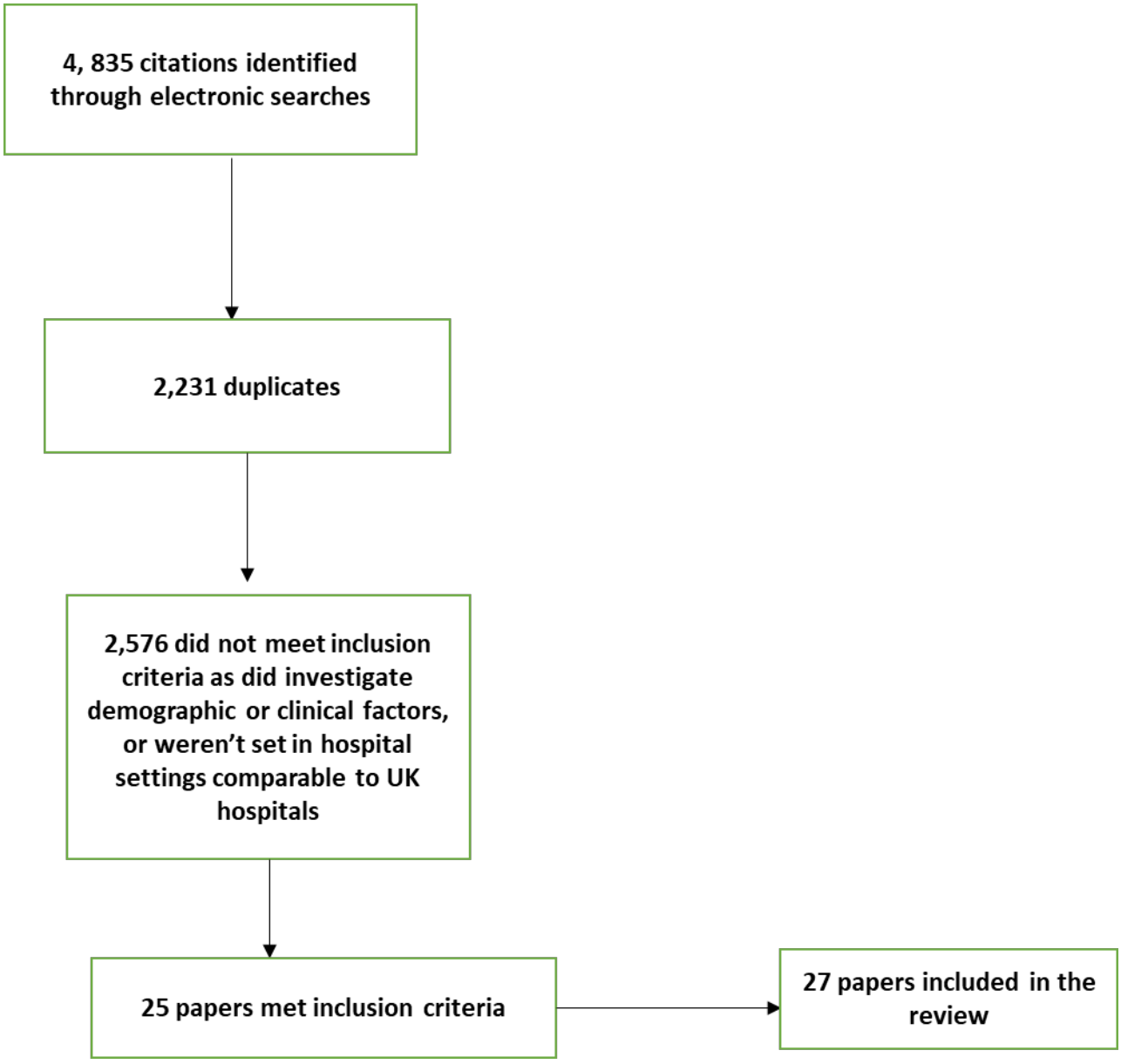


Figure 7: Flow diagram of included studies

Appendix Three gives an overview of the results given by each included paper.

2.4 Demographic Factors

2.4.1 Gender

9 studies explored the impact of gender as an influencing factor on the effectiveness of anti-VEGF therapy (Bloch *et al.*,2013; Chatziralli *et al.*,2014; Chrapek *et al.*,2015; Fang *et al*.,2013; Guber *et al.*,2014; Gupta *et al.*,2011; Holz *et al.*,2016; Singh *et al.*,2011; Van Asten *et al.*,2014). Of those, 9 did not find a statistically significant relationship between gender and visual outcomes. The only study that found gender to be a statistically significant factor in influencing visual outcomes was a 2014 study of 210 eyes from 192 patients (Gupta *et al*.,2011). They found that the mean change in RCRT at 6 months after their last injection in men *vs.* women was -6.47 (SE $\pm$7.18, p= 0.05), highlighting that males had a greater reduction in RCRT compared to females. This was the only paper that looked at the effect of gender on CRT rather than visual score, which may explain why it was the only study to find a significant factor or it could be a chance finding.

2.4.2 Age

12 studies explored the influence of age on the effectiveness of anti-VEGF therapy (Chatziralli *et al.*,2014; Chrapek *et al.*,2015; Fang *et al.*,2013; Gale *et al.*,2016; Guber *et al*.,2014; Gupta *et al.*,2011; Liew *et al.*,2016; Regillo *et al.*,2015; Rush *et al.*,2014; Van Asten *et al.*,2014; Ying *et al.*,2015;). Of those, 8 reported age to be a statistically significant predictor of visual outcomes. The overall trend was that the higher the age at baseline, the lower the visual outcome at time points of 1, 2 and 3 years. As it was not possible to combine the data from the studies to give a pooled effect size with associated confidence intervals, the studies with some of the biggest sample sizes have been highlighted in the text below and Figure 9 demonstrates the statistical significance of the findings by study size.

One of the studies with a sample size of 1,185 patients (Gale *et al.* ,2016) found a significantly higher odds of gaining $\geq$3 letters at 12 months for younger patients (aged 50-69 years) compared to older patients (>70) (p= 0.008). In another study of 500 patients (Regillo *e*t al.,2015), age was found to be a significant predictor of VA change at the year 2 time-point (-0.177, 95% CI -0.335 to -0.018), although this was reduced
at the year 1 time-point (-0.106, 95% CI -0.265 to 0.052). Age at first injection was found to be a non-statistically significant predictor of visual outcomes over 4 years

among 1,063 patients (Chrapek *et al.*,2015) (year 2: p= 0.126; year 3: p= 0.262; and year 4: p= 0.090 time-points).

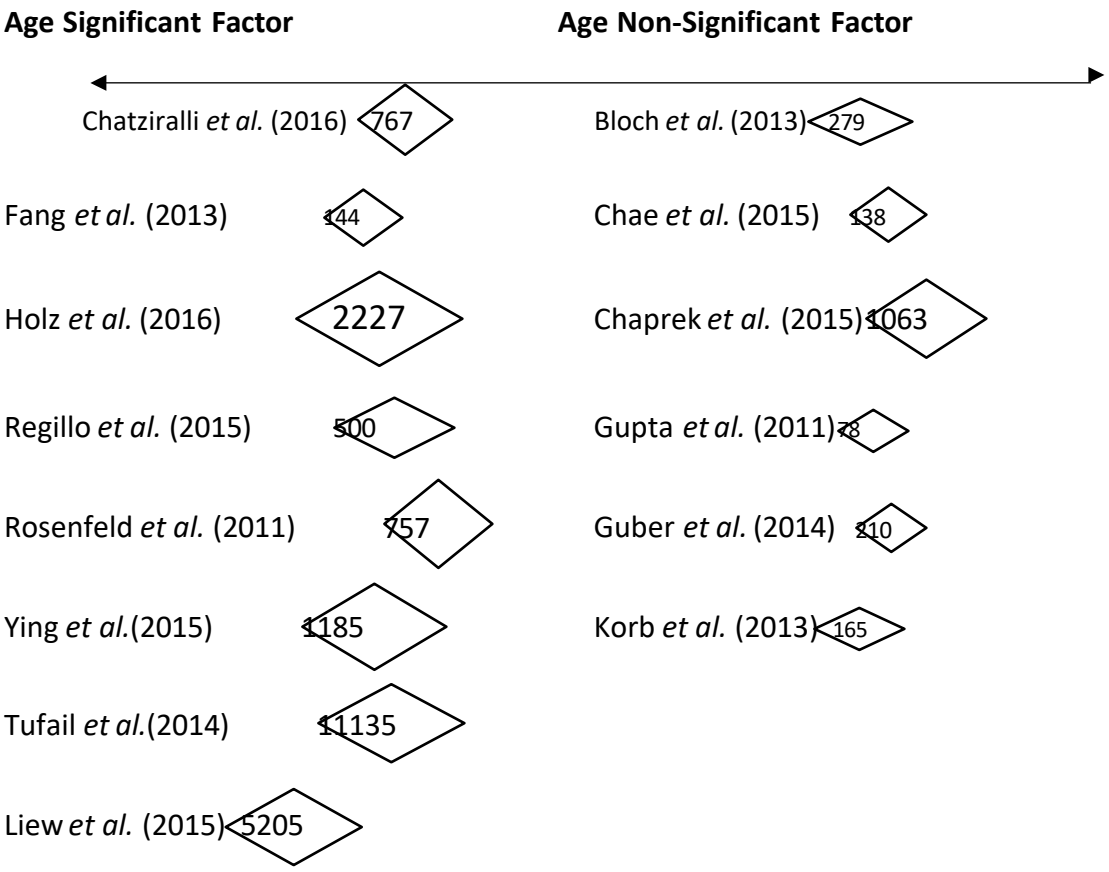


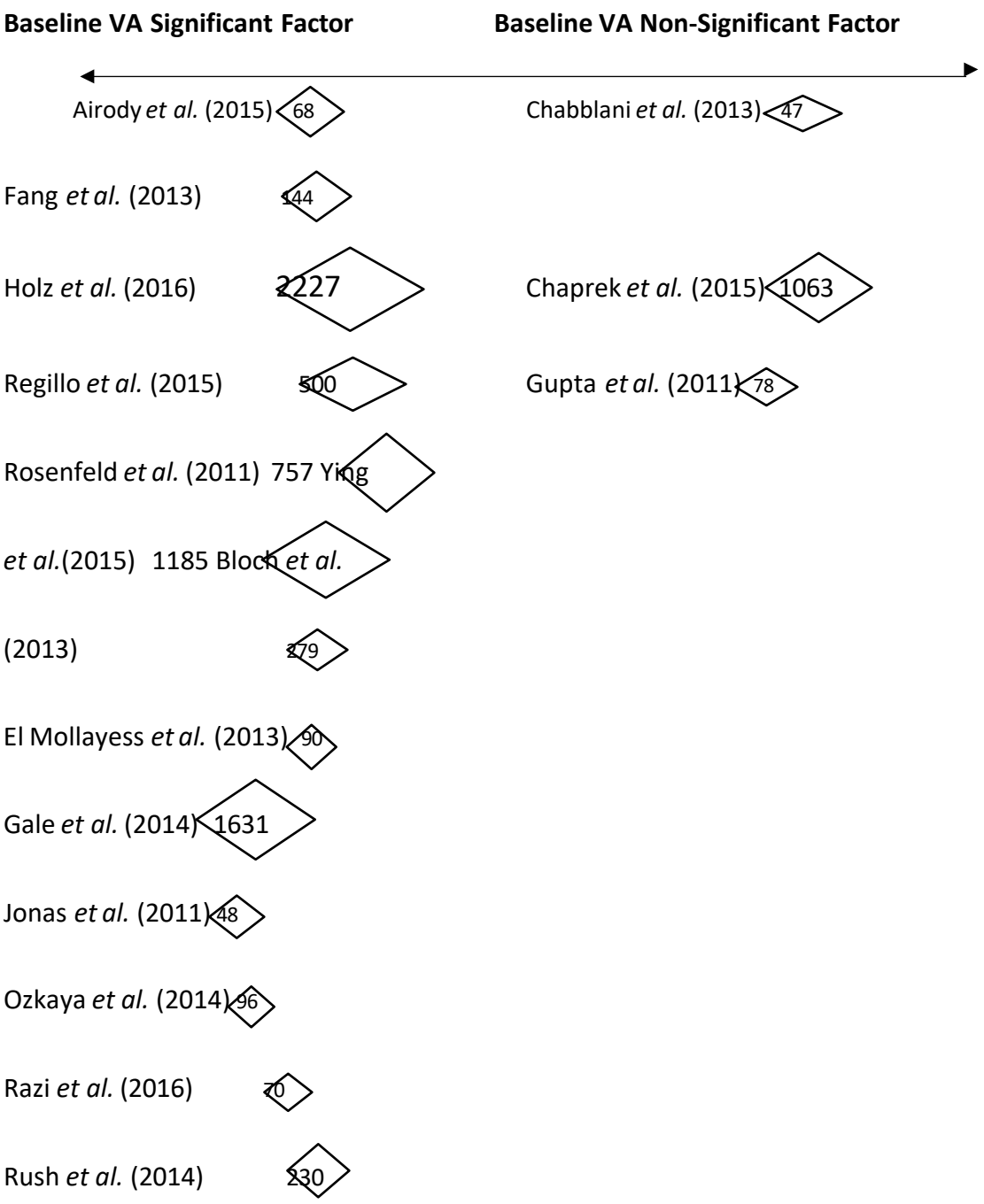
Figure 8: Sample sizes of studies that looked at age

2.5 Clinical Factors

2.5.1 Baseline VA or BCVA

17 studies explored the impact of baseline VA or BCVA on the effectiveness of anti- VEGF therapy (Airody *et al.*,2015; Chabblani *et al.*,2013; Chaprek *et al.*,2015; El Mollayess *et al.*,2013; 015; Fang *et al.*,2013; Gale *et al.*,2015; Gupta *et al.*,2011; Holz *et al.*,2016; Jonas *et al.*,2011; Ozkaya *et al.*,2014; Razi *et al.*, Regillo *et al.*,2015; 2016; Rosenfeld *et al.*,2011; Ying *et al.*,2015). Of these, 18 found baseline VA or BCVA to be a statistically significant

predictor of visual acuity at the later time point. The overall effect of baseline visual acuity on visual outcome was that the lower the baseline visual acuity, the lower the visual outcome would be at time points of 1 year and later. It was not possible to formally pool the data from studies; however, Figure 10 shows the statistical significance of the findings by study size. The study with one of the largest sample sizes, Regillo *et al.* (2015), of 2,227 patients found that baseline VA was a significant predictor of VA at both 1 year (-0.279 95% CI -0.352 to -0.206) and 2 years (-0.391,
95% CI -0.459 to -0.322).



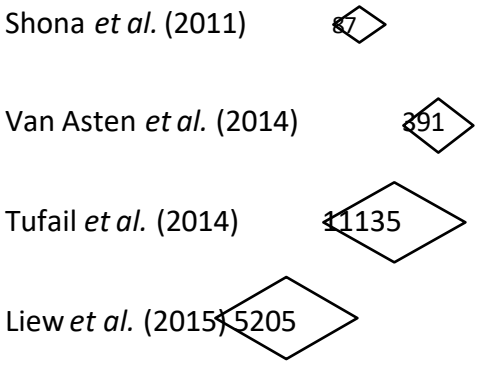
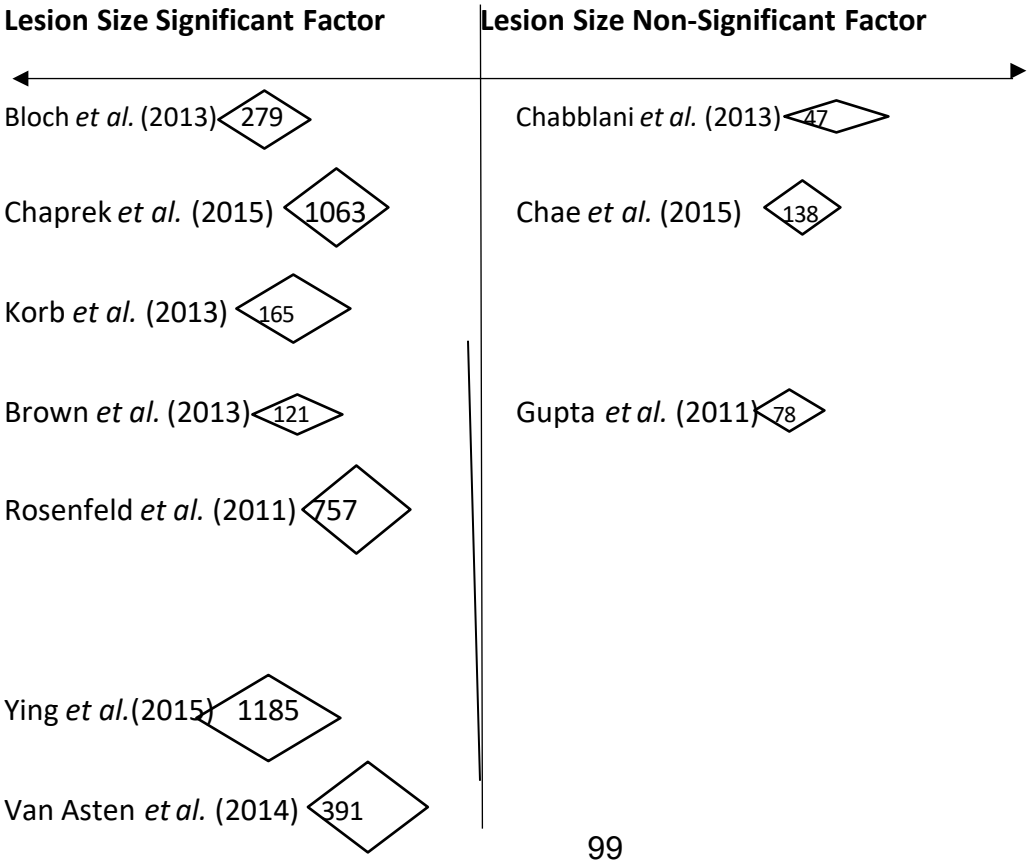


Figure 9: Sample sizes of studies that looked at baseline VA

2.5.2 Lesion size

Ten studies explored the impact of baseline lesion size on the effectiveness of anti- VEGF therapy (Chaprek *et al.*,2015; Chatziralli *et al.,*2016; Gale *et al.*,2016 Guber *et al.*,2014; Holz *et al.*,2016; Korb *et al.*,2013; Liew *et al.*,2016; NICE, 2018; Ozkaya *et al.*,2014; Ying *et al.,*2015). Of those, 7 found a significant relationship between lesion size and visual acuity; with smaller lesion size at baseline, the better visual acuity will be at time points longer than 12 months. Figure 11 shows the statistical significance of the findings by study size. The studies with some of the biggest sample sizes are highlighted in the text below.



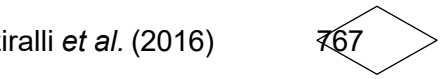


Figure 10: Sample sizes of studies that looked at lesion size

One study of 797 patients reported that the odds of BCVA ≥70 with a total lesion size <4 DA were 3 times the odds of those with a lesion size ≥4 DA and a BCVA of ≥70 at 12 months (Chatziralli *et al.,* 2016) (OR= 3.0, 95% CI 1.25 to 7.40). Similarly, Ying *et al.,* (2015) found that the patients with smaller baseline lesion areas would gain ≥3 letters at 12 months (patients with baseline area of CNV (mm^2) ≥2.54: OR 1.00; >2.54 to ≤5.08: OR 0.71 CI 0.47, 1.07, >5.08 to ≤10.2: OR 0.67, CI 0.38, 1.18, patients with baseline area of CNV (mm^2) that could not be measured: OR 0.44, CI 0.25, 0.76).

2.5.3 Number of injections

11 studies explored the impact of the number of injections on visual outcomes (Jonas *et al.,* 2011; Fang *et al.,* 2013; Shona *et al.,* 2011; Korb *et al.,* 2013; Regillo *et al.,* 2015; Calvo *et al.,* 2015; Chabblani *et al.,* 2013; Airody *et al.,* 2015; Chae *et al.,* 2015; Chatziralli *et al.*, 2016; Essex *et al.,* 2016). All of the studies found the number of injections to be a statistically significant predictor of visual outcomes with better outcomes for those receiving an average per year of 8 to 12 injections.

The study with the largest sample size (Regillo *et al.,* 2015) found that the number of injections was a statistically significant predictor for VA change at both years 1 (5.409, 95% CI 2.441 to 8.377) and 2 (1.933, 95% CI 0.852 to 3.015).

2.5.4 Lack of standardisation of reported data

The intention of this review was to identify factors that influence the effectiveness of anti-VEGF therapy. It was originally intended to pool the studies in a meta-analysis to quantify the magnitude of the individual factors on visual outcomes, however, given the poor reporting this was not possible. There was a lack of standardisation in the reporting of data in the included studies, with many not reporting results in enough detail. For example, 17 of the 30 papers included in this review simply presented *p*- values with no inclusion of mean values, standard deviations (SDs) (or information to calculate the SD). Therefore, a narrative synthesis of the evidence was undertaken.

2.6 Discussion

The main finding of this review was that the higher numbers of anti-VEGF injections received, the lower age at baseline and smaller lesion size at baseline were all factors that positively influence the effectiveness of anti-VEGF therapy in maintaining visual acuity. Higher visual acuity at baseline positively influenced efficacy of anti-VEGF therapy at longer time-points of at least two years. This review also found that age, visual acuity and lesion size at baseline were more likely to be detected in larger, international secondary reviews of clinical trial data, rather than in small, single centre retrospective studies. Higher age at diagnosis may lead to worse visual outcomes because older patients are less likely to still be able to drive and may therefore have difficulty getting to clinic often enough if they are relying on hospital transport, relatives or public transport to get to clinic.

It is noted however that there are some who would argue that studies of routine data, although much smaller in sample size, are more representative of real-world patient populations. Although this is a valid argument, collection of routine clinical data is unlikely to be of equal quality to secondary analysis of clinical trials. However, number of injections was detected as a significant factor in all types of studies, including smaller retrospective studies. The main findings of this review appear to be in keeping with the general body of literature on factors affecting visual outcome in nAMD.

The papers in this review suggest that the optimal number of injections for patients to avoid above average visual loss is 8-12 per year. However, many services may fail to deliver this due to high demand and shortages of resources/capacity to meet demand. It must also be asked whether better VA outcome leads to better patient reported outcomes. Do patients with better VA outcomes report better outcomes in terms of quality of life? This question is currently unanswered.

As described earlier, all of the included studies were of good quality. It is therefore concluded that the quality of the studies had no impact on the results of the review, but the variation in reporting of study outcomes did affect the ability of the review to use more statistical synthesis methods. The studies that were retrospective reviews of clinical trial data were rated as slightly lower quality than the prospective and retrospective studies of hospital data as the trial participants were potentially a selective sample of the study population. However, the trial populations did have larger sample sizes.

When considering all of the studies that looked at age together, there were some differences between those that found age to be a statistically significant predictor of visual outcomes, and those that did not. The studies that found age to be a statistically significant predictor of visual outcomes were largely international secondary analyses of multi-centre trial data, with large data sets of at least 500 patients in all but one study. The studies that did not find age to be a predictor were largely single centre retrospective reviews of routine data, with all but one study having sample sizes of less than 300. This suggests that larger sample sizes of at least 500 participants are needed to detect the effect of age on visual outcomes. It may also be linked to the fact that trial data tends to be more comprehensive and have fewer missing data then routine clinical data. However, despite their much bigger sample sizes, it could be argued that secondary analyses of trial data recruit patients according to strict inclusion and exclusion criteria, and therefore although studies of routine data tend to have much smaller sample sizes, they are more representative of real-world patient populations.

There were similar differences between studies that found baseline visual acuity to be a statistically significant factor and those that did not. Of the studies that found visual acuity to be a statistically significant factor, most had international study populations, were multi-centre, had large sample sizes, and many studies were secondary analyses of clinical trial data. The studies that didn't find baseline visual acuity to be a statistically significant factor were all retrospective studies of routine clinical data, were all carried out in only one country, and all bar one was single centre and had small sample sizes of less than 100. The one study that did have a larger sample size of 1063 and was multicentre was carried out in the Czech Republic. Therefore, it seems that larger sample sizes are required to detect the influence of baseline visual acuity, and that large international trial data is more likely to do this.

The difference between the studies that did not find lesion size to be a statistically significant factor and those that did is that those who did not find it to be a statistically significant factor were all retrospective studies of routine clinical data, with just 1-2 study centres in just one country. None of these studies had a sample size larger than 150. The studies that did find lesion size to be a statistically significant factor were again mostly larger, international studies of clinical trial data. Again, it also seems that the effect of lesion size at baseline is more likely to be detected in large, international, multi-centre clinical trials data, than in smaller retrospective studies of routine data. Figure 4 shows this distribution of studies and their sample sizes.

The fact that all the studies identified number of injections as a statistically significant clinical factor indicates that it had a highly detectable effect size, so that even smaller,

retrospective studies of routine data were able to detect it, not just large, international clinical trials data.

Throughout the review process, it was not possible to access one eligible paper, however, this is unlikely to have significantly changed the findings. It is possible that other eligible papers may have been missed during the screening process. This review is also limited by the inclusion of only papers that were published in English, which could have introduced bias. It is also limited by the fact that perhaps papers that did not have significant findings may not have published their work. However, attempts were made to search unpublished literature.

Although this review reported on age and gender, there was only one paper identified that looked at other demographic factors (e.g., smoking status, BMI and past medical history such as stroke and diabetes), none of which were found to be statistically significant. None of the included papers looked at socioeconomic status. This review is not examining the effects of individual anti-VEGF agents because there already exist a significant number of comparative head- to- head studies. This review similarly did not look at genetic factors, because this has already been well reported in current evidence. This review did aim to examine ethnicity, but there was insufficient evidence available to draw any conclusions.

Treatment regimen is modifiable and identifying factors which impact on early diagnosis, start date, length of treatment, and intensity may lead to improved outcomes. This poses questions around whether more needs to be done to diagnose nAMD cases and start treatment promptly. Current guidelines recommend that on diagnosis of nAMD, treatment should be commenced within two weeks (NICE, 2019). This review also identified number of injections as a modifiable factor, which also poses questions around whether service provision is currently adequate, and whether improvements to service provision are required in terms of capacity, demand and accessibility. These modifiable factors also pose questions to clinicians around whether addressing such factors has any impact on reported quality of life for these patients. These matter, because if addressing factors that affect visual outcome does not lead to improvements in quality of life, it could lead to future consideration of allocation of resources. However, there may also be more modifiable factors that were not included in the studies. The results of this review highlight the importance of patients receiving early anti-VEGF injections to achieve the best possible visual outcomes. This means that the role of the factors studied in this review play in variation in visual outcomes in patients with nAMD need to be investigated and addressed in future research. Future research must also address the need for more

standardisation in how observational studies in the field of nAMD are reported. There are a number of unanswered questions:

- Are there more modifiable factors that influence the effectiveness of anti-VEGF therapy?
- What can be done to improve early access to diagnosis and treatment, and to address any gaps in service provision?
- Does variation in VA outcome affect quality of life?
- Does ethnicity or socio- economic status affect visual outcome?

2.7 Conclusions

This review has demonstrated that there is some evidence of clinical and demographic factors that affect the effectiveness of anti-VEGF therapy and hence variation in VA outcome. It found that better visual acuity at baseline, smaller lesion size, lower age at baseline, and receiving at least 8 injections per year resulted in better visual outcomes for patients with nAMD being treated with anti-VEGF therapy. However, this review was unable to identify as wide a range of factors as was hoped and was unable to formally pool the studies in a meta-analysis.

The results also highlight the importance of ensuring timely diagnosis and commencement of treatment, and in ensuring adherence to treatment regimens.

Now that it has been established from the literature that visual acuity at baseline, age at baseline, and number of injections received are significant factors on better visual outcomes with anti-VEGF treatment, further work needs to be undertaken to identify factors that were not found in the systematic review. In the next chapter, these wider set of factors are explored through utilising a large real-world dataset. This will be a means of further understanding variations in visual outcomes.

3.0 Variations in Visual Outcomes in Neovascular Macular Degeneration and their Causes: A Retrospective Analysis of Medisoft Data

3.1 Introduction

As discussed in Chapter 2, age at baseline, number of injections and visual acuity at baseline contribute to the success of anti-VEGF treatment for nAMD. However, it was not established what impact factors such as ethnicity, smoking or social deprivation has on the success of treatment. To explore such factors an analysis of a real-world dataset will be undertaken. This chapter outlines the methods and findings.

3.2 Background to Medisoft data

The data used in this study came from an Electronic Medical Records (EMR) database managed by a company called Medisoft. In 2021, there were 80 ophthalmology departments across the UK that use this EMR system as part of their nAMD pathway. This system records information on:

- Age in years and months at the time of first EMR entry for nAMD.
- Age in years and months at the time of first intravitreal injection of anti-VEGF drugs for nAMD.
- Gender.
- Visual acuity (measured in both ETDRS letter score and Snellen) for both eyes
- The time of first injection and at each prior or subsequent assessment visit.
- Date of each subsequent assessment / injection visit.
- Re-treatment criteria, decision and if relevant reason(s) for permanently stopping treatment.
- Details of the injection process (including indication for injection, drug used, dose, site, anaesthesia used, and complications).
- Defined clinical examination findings at each visit related to neovascular AMD.
- Date of other ophthalmic procedure or investigation performed during follow up (ocular surgery, or procedures, retinal imaging, blindness registration).
- Grade and job title of the person administering the injections and recording the

assessment data.

- Whether treatment was initiated elsewhere, or part of the treatment occurred at another centre.
- Documented cardiovascular events or other intercurrent illness documented in the ophthalmic EPR record during the follow up phase.
- Selected systemic information (where available) relevant to the incidence or progression of nAMD, or mortality or cardiovascular/cerebrovascular disease e.g., type of diabetes, duration of diabetes, HbA1c, cardiovascular risk factors (where available).

Medisoft were contracted to extract and anonymise the data and transfer it electronically to the author of this thesis.

3.3 Data Management

3.3.1 Ethical Approval

Health Research Authority (HRA) and Health Sciences Departmental Research Governance approvals were sought, and approval granted in December 2018.

3.3.2 Approaching sites

Sites known to contribute data to the EMR system as part of their nAMD pathway were invited by letter to access their data. Sites were selected to take part based on the members of the AMD users' group (Tufail *et al,* 2014). Written consent was required from the medical retina lead and Caldicott Guardian at each site for their EMR nAMD data to be extracted and used as part of the study. Figure 11 gives a flow diagram of the recruitment process. There were three inner city teaching hospitals, and the other four sites were district hospitals.
All eligible sites who were using the EMR system were approached to take part in the study. No sites were excluded. Sites were only not included if they declined to take part or failed to reply.

Figure 11: Recruitment Process Flowchart Diagram

3.3.3 Extraction of Data

Copies of signed consent forms from participating sites were sent to Medisoft, who extracted and anonymised the data from these sites, which dated from 2008 to 2017. They were then transferred electronically in a password protected electronic link, as comma-separated values (CSV) files. These files were then imported into Stata version 15, with the later data analysis taking place in Stata version 16. Data were stored securely on a University of York's networked drive with password protection and never stored on any temporary media. No personal identifiable information was sent or used as part of this study. On receipt of the data, it was processed in accordance with the Data Protection Act 1998. The data were extracted during December 2018. The cleaning process took place between January 2018 and August 2021. It is common in ophthalmic research to count both number of eyes and patient numbers. Therefore, this is why both patient numbers and numbers of eyes has been reported in this analysis. At each site A to G, there were a total of 5,013 patients (473 eyes), 1726 patients (2,720 eyes), 1726 patients (2,095 eyes), 1,457 patients (2,133 eyes), 875
patients (1,037 eyes), 2,583 patients (3,911 eyes) and 905 patients (1,337 eyes).

3.4 Data Management

3.4.1 Cleaning and merging

The files were received as separate text files for demographics, medical history, cataract surgery history, ocular medical history, visual acuity, injection history, injector grade history and injected drug history. Each was imported into Stata version 15 and variables reformatted where necessary. During the merging process, several decisions had to be made about the data. One of these was how to identify which VA assessment belonged to which study time point, as the VA assessments occurred with differing regularities. It was decided that the nearest VA assessment to each study time point would be used, as long as it was within two weeks either side of the time point. If two VA assessments were present two weeks either side of the time point, the assessment in the two weeks after the time point was used. The baseline VA assessment was identified as the nearest assessment that took place before the first anti-VEGF injection.

The cleaning process of this large dataset was extremely challenging. It was originally planned to spend three months cleaning the data. However, due to the complexity of the cleaning process, even with the advice and assistance of two statisticians, the cleaning process actually took over two years, in conjunction with COVID-19 and the other elements of this thesis. This clearly had a serious impact on the time available during the PhD to complete this retrospective study. The cleaning process took so long because large amounts of cleaning code were required to be able to successfully merge files into a final master dataset (see Figure 12 for an example of some of the coding for the exclusions file). There was on average 300 – 350 lines of Stata Do-File coding for each file, and there were 12 finalised cleaning codes after trial and error. This was so difficult because each separate file had to be completely reformatted, before being matched with the right patient and eye, and a lot of coding was needed to destring relevant variables, and better organise categorical variables, for example. A very methodical approach was therefore required to do this, whilst making sure that the right data was kept whilst applying the correct exclusion criteria. New variables also had to be generated from the originals, for example a new variable calculated to have VA scores for the relevant time-points, or to calculate a variable that identified only patients that had not had cataract surgery within three months of being included in the study. A new variable also had to be calculated to match injection number with their nearest VA score date. This was further hampered by the fact that when experimenting with running codes, running them could take up to 20 minutes at a time, due to the sheer volume of data.

```
use "Y:\Medisoft Data\Files\FinalData\diag.dta", clear

* Identify and isolate BRVO

tab diagnosisdescription
keep if diagnosisdescription=="branch retinal artery occlusion" ///
| diagnosisdescription=="branch retinal artery occlusion with a visible embolus" ///
| diagnosisdescription=="branch retinal vein occlusion" ///
| diagnosisdescription=="branch retinal vein occlusion with disc collaterals" ///
| diagnosisdescription=="branch retinal vein occlusion with macular ischaemia" ///
| diagnosisdescription=="branch retinal vein occlusion with macular oedema" ///
| diagnosisdescription=="branch retinal vein occlusion with retinal collaterals" ///
| diagnosisdescription=="macular branch retinal vein occlusion"

tab diagnosisdescription

    * Check duplicates

        * Identical records

duplicates tag patientid eyecode diagnosisdate diagnosisdescription , gen(dup) bys patientid eyecode
diagnosisdate diagnosisdescription ,: gen num = _n

tab dup
list patientid eyecode diagnosisdate diagnosisdescription dup num if dup > 0

* okay to delete
drop if num > 1 & dup > 0 drop dup num

        * Same diagnosis on different dates

duplicates tag patientid eyecode diagnosisdescription , gen(dup)
bys patientid eyecode diagnosisdescription (diagnosisdate) ,: gen num = _n
```

Figure 12: Example of cleaning code for exclusion cleaning file

3.4.2 Real-world data

While data from RCTs have an established place as the gold standard in medical research, there is increasing appreciation of both the role and use of real-world data (RWD) (Dreyer and Garner, 2009; Holz *et al.,* 2013; Kim and Kim, 2018; Kim *et al.,* 2018; Talks *et al.*, 2019). RCT data provides standardised efficacy outcomes, but often lacks the ability to provide information on long-term effectiveness in everyday clinical settings. The Luminous study, for example, enrolled 30,138 patients, to investigate the safety and efficacy of Ranibizumab treatment, over 5 years in both treatment-naïve and treatment exposed patients (Hamilton *et al.,* 2020). However, despite being the largest real-world study investigating ranibizumab treatment for nAMD, it did not produce any new safety or efficacy findings. Therefore, RCT and RWD data should be seen to have a complementary rather than a mutually exclusive relationship (Kim *et al.*, 2018). The last two decades has seen growth in the numbers of large registries and electronic medical record (EMR) systems being used as part of routine clinical care. This should in theory mean rapid access to large data sets for use in research. However, the fact that EMR data was not originally designed for use in research, can mean that it has pitfalls and problems that need to be overcome when used for this purpose (Kim and Kim, 2018; Beaulieu-Jones, 2018). Some of these will be identified and discussed from the experience of data cleaning in this study.

The earliest difficulty with the EMR dataset that was encountered was the sheer size and volume of the data. Before ineligible cases were excluded, the dataset had 226,909 unique treatment episodes, 1,598,143 unique visual acuity assessments and 25,142 patients. This meant that trialling code to clean and merge individual data files was a slow and time-consuming process. Although data were primarily reviewed site by site to speed this process up, when it was necessary to combine all the data, Stata processing was very slow even for simple steps. As a PhD student, with little experience of analysing large datasets, this was very daunting. The high number of observations in this dataset was due to not only the number of individual patients, but also the fact that many of these patients had visits and treatments recorded several times a year, for up to 10 years, with varying amounts of clinical information recorded at each observation point.

Although missing data is an issue for all types of studies, including RCTs, this is more pertinent in EMR data (Beaulieu-Jones *et al*., 2018) and the EMR data in this study was no exception to this. Due to the dataset being designed to produce an automated letter and avoid the need for paper-based records, rather than the completeness of research datasets, it is unsurprising that often minimal data is recorded per visit. Missing data also led to the problem of deciding on ways to manage it, without introducing bias.

The inherent nature of the EMR dataset being completed by clinicians in busy nAMD clinics, rather than by researchers in controlled circumstances, means that data entry errors were inevitable. EMR data, although large, is often unstable with serious errors, with the ability of the dataset to allow free text complicating the issue. Where data entry errors were suspected, it was often difficult to be sure that it was indeed a data entry error, or an unexpected medical history or treatment pattern.

Although EMR can provide large amounts of data, the time spent on data cleaning was further added to by the presence of data that was not useful. The nature of EMR data being collected for clinical rather than research purposes often lead to large amounts of data not relevant to the research question being removed (Kim and Kim, 2018). Whilst this was expected, there were many observations that appeared to be unnecessary. For example, it often occurred that if a patient had a history of heart disease recorded, this would be re-recorded at every visit they had, with patients having up to 143 visits. Recent MI is a relative contraindication for anti-VEGF administration, so this contributes to making the database messy for research purposes.

3.4.3 Exclusion criteria

Eyes with central retinal vein occlusion (CRVO), BRVO, traumatic eye injury and cataract surgery within 3 months were excluded from the analysis. The reasons for this are detailed in Table 4. The exclusion criteria were identified from the retrospective dataset.

Exclusion Criteria	Reason
CRVO diagnosis	Eye may already be being treated with anti-VEGF for CRVO, so difficult to attribute any visual effects purely to treatment for nAMD.

BRVO diagnosis	Eye may already be being treated with anti-VEGF for CRVO, so difficult to attribute any visual effects purely to treatment for nAMD.
Traumatic eye injury	Eye injury could lead to decreased visual acuity that makes it difficult to understand the effects of anti-VEGF therapy for nAMD.
Cataract surgery within 3 months	Recent cataract surgery can lead to increased visual acuity, so would be difficult to tell if any changes in visual acuity were due to the cataract surgery or anti-VEGF treatment for nAMD.

Table 4: Reasons for exclusion criteria

3.4.4 Study demographic factors to be analysed

Demographic factors to be analysed in the analysis were *a priori* decided upon (see Table 5 below).

IMD score: a score from 0 – 100 (shows the amount of social deprivation, with a score of 0 representing the least deprivation)	**IMD decile:** ordinal categories from 1- 10 (ranks local authority area of patients in order of levels of social deprivation, with 1 having the least social deprivation).
Smoking status: current smoker, ex-smoker, never smoked.	**Age:** age in years at time of first EMR entry
Ethnicity: ethnicity category expressed by patient	**Bilaterality:** a patient having or developing two eyes with nAMD.

Table 5: Demographic factors to be analysed

The over-arching theme of this thesis was to add to the wider knowledge of and understanding of healthcare inequalities; and this retrospective study aimed to do this by identifying and explaining reasons for healthcare inequalities, in nAMD. However, it is acknowledged that the reasons for variation are multifactorial, including service design, capacity and access to healthcare. It was therefore decided *a priori* which factors would be best placed to do this. This was based on the findings from the previously completed systematic review in chapter two of this thesis, which helped to

identify known and unknown factors as described below, and which factors were controlled for in the models.

Known factors:

3.4.4.1 Gender: it was found by the systematic review earlier in this thesis that gender does not have a significant impact on visual outcome, so was not analysed in any regression models.

3.4.4.2 Age: it was found from the review that higher age at baseline led to poorer visual outcomes. Although age as a patient characteristic was not planned to be analysed in any regression models, it was deemed important to be able to describe the age profile of the patients in the dataset.

3.4.4.3 Baseline VA: it was clear from the systematic review that baseline VA had a strong impact on visual outcome in the short and long-term. It was therefore decided not to explore this as a characteristic of interest in the models in this study.

3.4.4.4 Number of injections: the review also found that number of injections had a significant impact on visual outcome. However, it was decided to investigate how patient characteristics were associated with number of injections received.

Factors with limited evidence:

3.4.4.5 Other health conditions such as diabetes, heart disease and diabetes: although the systematic review was unable to find any data on such factors, after cleaning of the retrospective data it became clear that due to insufficient data on such factors, it would be unable to run any models on them in this analysis.

3.4.4.6 Smoking: the systematic review was unable to find any data on the impact of smoking on visual outcome, so this was included in analyses.

3.4.4.7 Social deprivation: there was similarly no data from the review on how social deprivation affected visual outcomes and number of injections received, so it was decided to include this patient characteristic in the analysis.

3.4.4.8 Ethnicity: the review was unable to find significant data on how ethnicity affected visual outcome.

3.4.4.9 Bilaterality: it was unknown from the systematic review whether developing nAMD in two eyes affected visual outcome long-term.

The first of these was social deprivation, using IMD score. There was consistent data provided for this. Current literature on healthcare inequalities in general, such as The Lord Carter Report (2015), strongly suggest that social deprivation does affect access to healthcare, so it was decided to analyse how social deprivation affected number of injections received. As explained earlier in this chapter, the NICE guidelines recommend three injections in the first three months of starting treatment for nAMD (Royal College of Ophthalmology, 2017). As social deprivation has been described at site level, it was prudent to investigate how average social deprivation affected compliance with guidelines at site level. As having two eyes being treated for nAMD is associated with poorer visual outcomes, social deprivation, in the form of IMD Decile was analysed to investigate whether social deprivation is associated with patients developing nAMD in 2 eyes, and therefore being more likely to have poorer visual outcomes. It has been found in some studies that smoking is associated with an increased risk of developing nAMD. Because of this, it was of interest to investigate whether smoking led to poorer visual outcomes in this sample. Literature on health inequalities, such as The Lord Carter Report (2015), also suggest that ethnicity has a significant effect on poorer health outcomes in general. It was therefore significant to investigate whether this was the case in this subset of patients with nAMD. It was *a priori* decided to also see how ethnicity and visual outcome interacted with social deprivation.

3.5 Aims

- To establish how much variation in letterscore, LogMar, number of anti-VEGF injections received and compliance with guideline recommendations of the number of injections (3 and 12 months) can be explained by social deprivation.
- To establish how much variation in patients developing bilateral nAMD can be explained by IMD Decile.
- To establish how much variation in visual loss of >15 letters can be explained by smoking status.

3.6 Methods

The relationship between visual outcome (measured in letter score or LogMar) and social deprivation (measured in IMD score) will be explored using a covariance pattern mixed-effect linear regression model, because letterscore is a repeated measure. Bilaterality, smoking and ethnicity will be included as fixed effects. Because of the very low numbers of non-white patients in the sample (2.2%), different non-white ethnicities were all grouped into one category. It is recognised that this does not reflect differences between the different groups. Eyes were clustered by patient in the model, as it was felt that where two eyes in the analysis came from the same patient, they were more likely to be more similar than two eyes from two different patients. Variable coefficients, 95% confidence intervals and *p*-values will be reported. Because site G did not measure visual acuity in letterscore, but in LogMar, in order to see if visual outcomes were particularly different at site G compared to other sites, LogMar measurements at all sites were converted into letterscore. Site G was then included in an analysis of all sites.

The relationship between number of injections received and social deprivation (measured in IMD score) will be explored using a Poisson regression model. A Poisson regression model was used because the number of injections variable was count data over varying periods of time in the study between patients. Bilaterality, ethnicity and smoking will be controlled for and included as fixed effects and eyes as a random effect. The relationship between compliance with the recommended number of injections at three months (3 injections), and 12 months (8 injections) will be explored using odds ratio models. The relationship between bilaterality and IMD Decile will also be explored using a logistic regression model, controlling for ethnicity and smoking as fixed effects and eyes as a random effect. The relationship between smoking and vision loss of >15 letters will be explored using an odds ratio model controlling for ethnicity and IMD Score as fixed effects and eyes as a random effect.

3.7 Results

3.7.1 Descriptive statistics

One of the categorical variables used in the models was; how many people had both of their eyes or just one of their eyes treated for nAMD in the study. Nearly 70% of patients in the study only had one eye being treated for nAMD. This shows a similar distribution of patients with only one eye being treated for nAMD, with Site E having a particularly high proportion of patients

being unilateral (84.4%). There were nearly twice as many females as males in the sample (see Tables 7 and 8 for further information). This is likely to be because females generally tend to live longer than males and hence are more likely to have nAMD (Hamilton *et al.,* 2020). This distribution was largely reflected at site level. Data on IMD score were available for 10,663 cases in the dataset. This score can range from 0-100. No one in the dataset scored the top range of IMD score. The mean IMD score across all sites was 20 (see Figures 13-17 for further information). However, there was a very large range, of more than 80. Between sites, Site E had the lowest mean IMD score (10), therefore having the least amount of social deprivation. Site E also had the lowest standard deviation, with its highest level of social deprivation only reaching 40. Site C had the highest mean score, but site D had the highest range (80). The variable is positively skewed, with the majority of values being under 40. This suggests that overall, more than half of patients in the whole dataset are in the lower half of IMD scores. Each site was positively skewed. It is also recognised that Figure 16 shows a more significant amount of variation in visual acuity at Site G, and this could be due to either a smaller sample size at Site G, or the fact that LogMar scores were transformed into ETDRS equivalent. Site G was the site with the smallest number of patients. This could be meaningful in terms of it's irregular visual outcome pattern.

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Figure 13 below shows the IMD score for all sites.

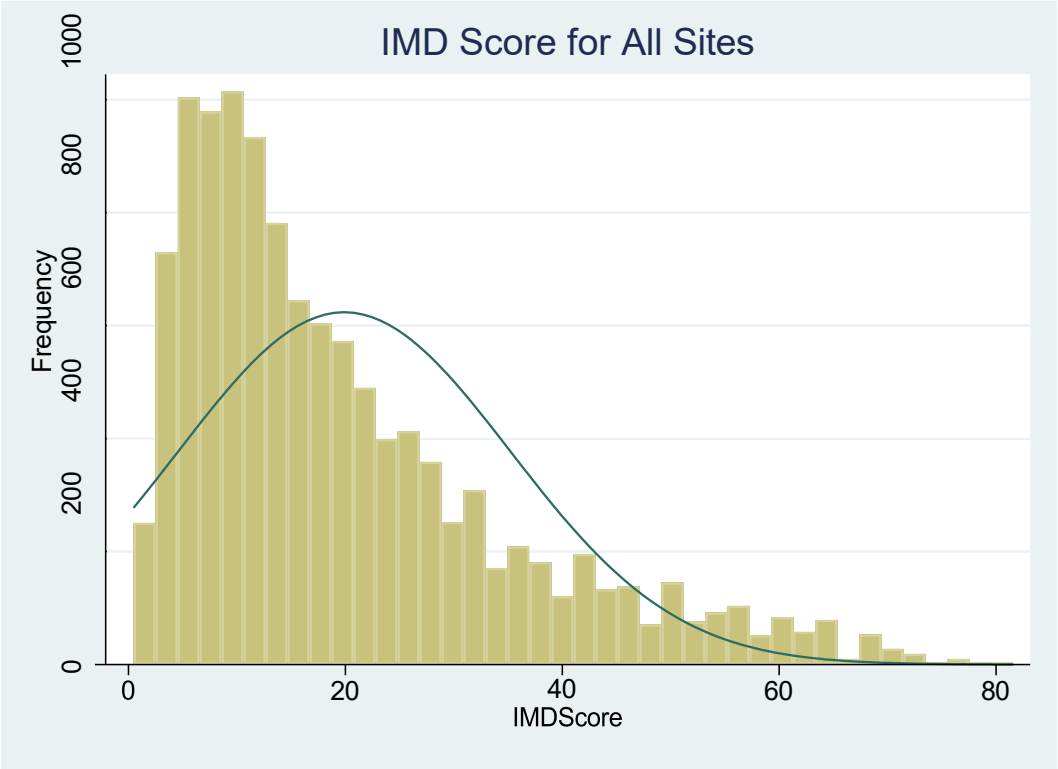

Figure 13: Frequency distribution for IMD Score

Figure 14 shows IMD score by site.

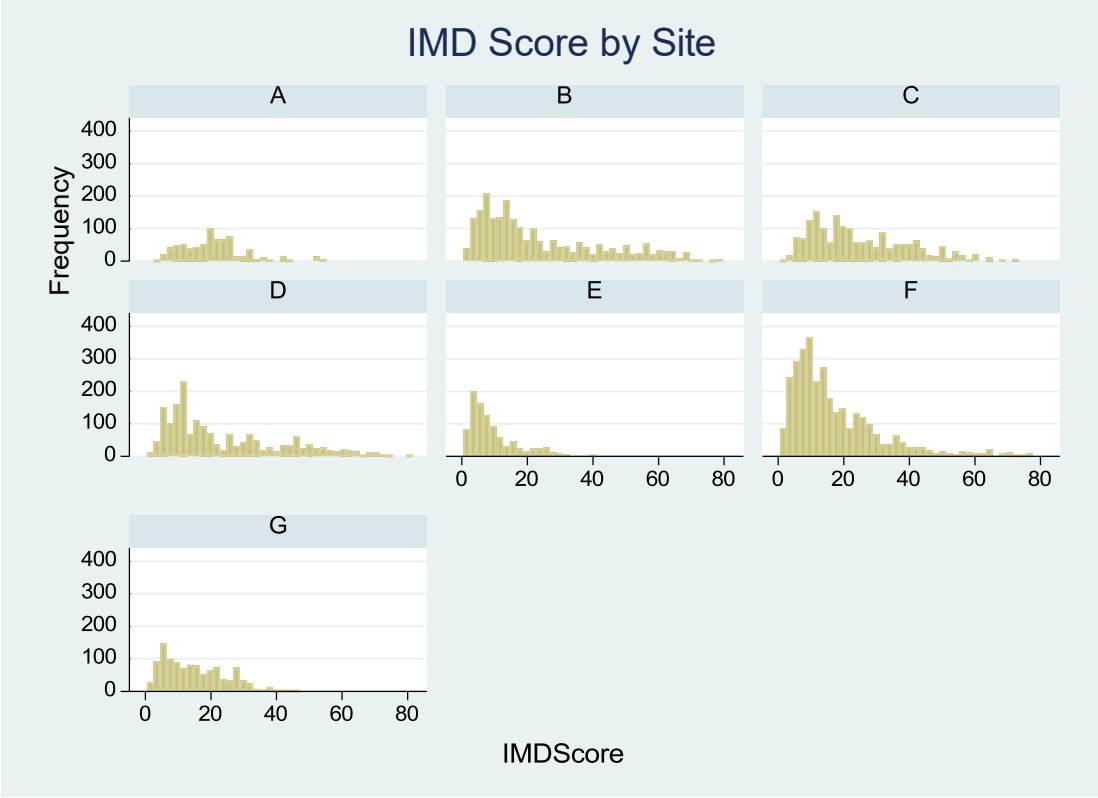

Figure 14: Frequency distribution of IMD Score by site

Table 6 shows demographic data of each site.

Siteid	Unilateral (%)	Bilateral (%)	Total Number of Eyes	Gender (%)	Mean IMD Score	Median IMD Score	IMD Score Standard Deviation	IMD Score Range	IMD Score Interquartile Range
Site A	606 (70.5)	254 (29.5)	860	Female:450 (61.4) Male: 283 (38.6)	20.6	19.9	9.5	2.7, 54.2	5.4, 54.2
Site B	1,726 (63.5)	994 (33)	2,720	Female: 1,362 (61.3) Male: 861 (38.7)	23.5	16.6	18.3	1.2 ,78.3	1.2, 78.3
Site C	1,401 (66.9)	694 (33.1)	2,095	Female: 1,108 (63.4) Male: 640 (36.6)	24.9	21.1	14.6	2.4, 72.7	4.0, 72.7

Site D	1,457 (68.3)	676 (31.7)	2,133	**Female:** 1,137 (63.3) **Male:** 658 (38.7)	23.8	17.0	17.6	1.9, 81.6	1.9, 72.9
Site E	875 (84.4)	162 (15.6)	1,037	**Female:** 581 (60.8) **Male:** 375 (39.2)	9.4	7.3	7.3	0.5, 40.2	0.6, 32.2
Site F	2,584 (66.1)	1,328 (34.0)	3,912	**Female:** 2,044 (62.9) **Male:** 1,204 (37.1)	17.3	13.1	13.8	1.2, 77.5	1.2, 77.5
Site G	905 (80.7)	216 (19.3)	1,121	**Female:** 714 (63.7) **Male:** 407 (36.3)	14.9	14.9	9.2	1.0, 45.6	1.7, 42.3

All sites	14,094	11,824 (83.89)	2,270 (16.11)	**Female:**7,396 (62.6) **Male:** 4,428 (37.5)	20.4	15.5	15.7	0.5, 81.6	8.7 27.8

Table 6: Bilaterality, Gender and IMD Score information by site

Figure 15 shows the mean visual acuity over time.

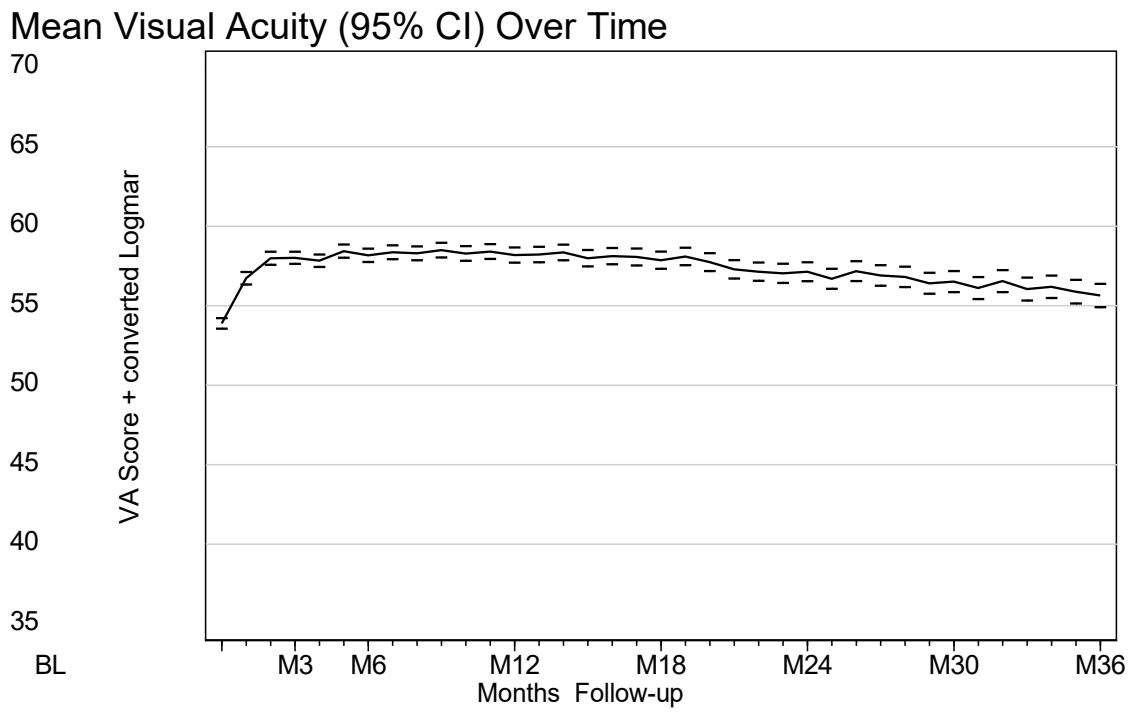

Figure 15: Visual acuity at all time-points

Figure 16 shows VA over time by site.

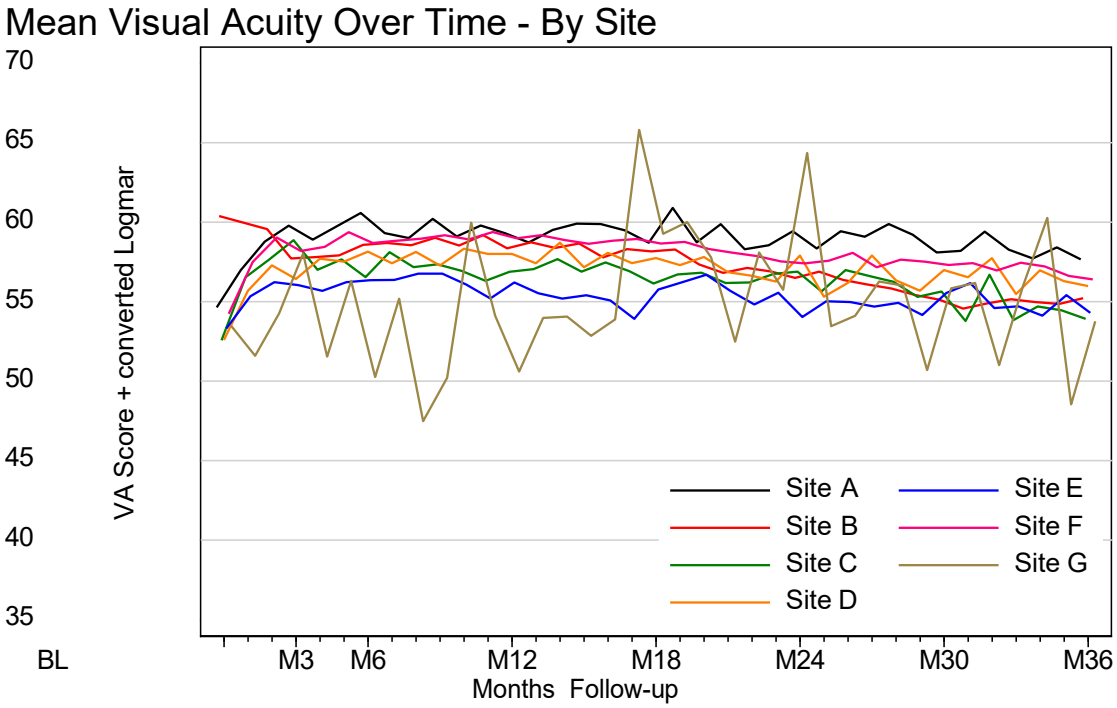

Figure 16: Mean visual acuity at all time-points by site

Figure 17 shows VA according to IMD.

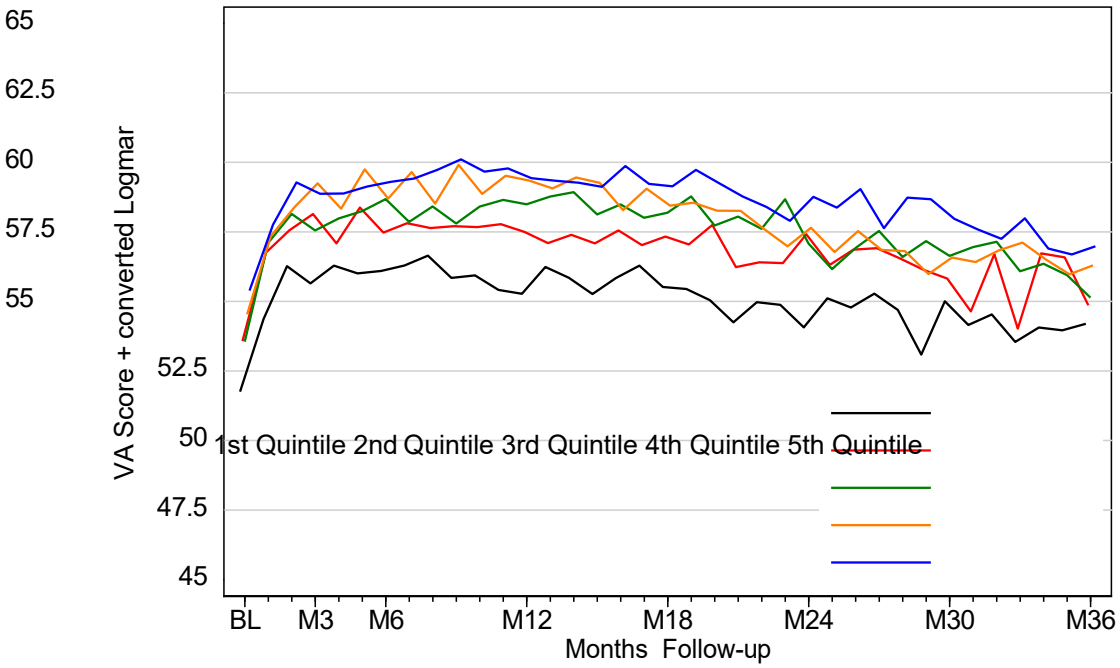

Figure 17: Mean visual acuity at all time-points by IMD decile quintiles

Table 7 shows VA score at each site.

Site ID	VA Baseline (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 3 (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 6 (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 12 (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 18 (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 24 (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 30 (Letterscore) (Mean, SD, Range, Number of Eyes)	VA Month 36 (Letterscore) (Mean, SD, Range, Number of Eyes)
Site A	54.6 14.7 1-85 **n=7611**	59.8 15.7 0-85 **n=544**	60.5 17.2 11- 85 **n=359**	59.3 18.5 0-85 **n=286**	58.7 17.3 0-85 **n=250**	59.5 18.5 0-85 **n=205**	57.9 19.3 3-85 **n=152**	57.6 19.2 1-85 **n=128**
Site B	60.4 15.6 0-95 **n=524**	57.7 17.3 0-94 **n=1,512**	58.6 17.3 0-94 **n=1,207**	58.4 17.2 0-85 **n=979**	58.2 17.5 0-91 **n=815**	56.5 18.7 0-95 **n=739**	55.1 18.7 0-85 **n=582**	55.2 19.6 0-85 **n=527**
Site C	52.4 14.6 0-83 **n=1,976**	58.8 15.4 1-85 **n=1,253**	56.5 16.9 0-85 **n=1,012**	56.9 17.6 0-85 **n=925**	56.0 18.5 0-85 **n=768**	56.7 18.2 0-85 **n=665**	55.4 18.2 0-85 **n=507**	54.0 19.3 0-85 **n=437**

Site D	52.7 15.9 0-85 **n=1,621**	56.9 17.6 0-85 **n=718**	58.2 16.9 0-85 **n=990**	58.3 18.1 0-85 **n=777**	58.1 18.4 0-86 **n=616**	58.5 19.3 0-85 **n=510**	57.0 20.5 0-85 **n=430**	56.2 20.4 0-85 **n=342**
Site E	53.2 19.2 0-95 **n=521**	56.0 19.3 0-85 **n=447**	56.4 19.5 0-85 **n=417**	56.2 20.6 0-90 **n=328**	55.7 21.3 0-85 **n=250**	54.0 22.6 0-85 **n=241**	55.5 21.6 0-87 **n=211**	54.3 21.9 0-88 **n=166**
Site F	54.2 16.7 0-85 **n=3,365**	58.2 17.3 0-91 **n=3,103**	58.5 17.5 0-87 **n=2,612**	58.9 17.9 0-86 **n=2,174**	58.5 18.8 0-85 **n=1,841**	57.3 19.0 0-85 **n=1,555**	57.1 19.3 0-85 **n=1,350**	56.2 19.6 0-85 **n=1,169**
Site G (Converted LogMar Score)	53.5 18.7 0-85 **n=100**	54.9 19.2 0-85 **n=100**	54.9 20.4 0-85 **n=73**	52.8 20.6 5-80 **n=68**	56.6 22.3 0-85 **n=55**	56.6 22.3 0-85 **n=53**	53.0 16.2 5-80 **n=44**	50.8 23.0 0-81 **n=41**

Table 7: Letterscore by Site

Table 8 shows VA change at each site.

Site ID	VA Change Month 3 (Letterscore) (Mean, SD, Range)	VA Change Month 6 (Letterscore) (Mean, SD, Range)	VA Change Month 12 (Letterscore) (Mean, SD, Range)	VA Change Month 18 (Letterscore) (Mean, SD, Range)	VA Change Month 24 (Letterscore) (Mean, SD, Range)	VA Change Month 30 (Letterscore) (Mean, SD, Range)	VA Change Month 36 (Letterscore) (Mean, SD, Range)
Site A	4.1 9.7 -46-36	4.4 11.3 -48-40	3.8 14.1 -62-42	3.7 15.0 -56-47	3.2 16.1 -52-49	59.5 18.5 0-85	57.9 19.3 3-85
Site B	-1.0 11.5 -55-43	-8.0 12.0 -46-36	-2.5 13.8 -68-38	-4.2 14.1 -59-38	-6.1 15.7 -63-32	-7.4 16.2 -63-30	-8.7 18.8 -77-26
Site C	5.6 10.3 -46-49	5.1 12.0 -68-49	4.6 13.9 -68-55	4.0 15.0 -68-44	3.3 15.4 -68-48	1.8 16.5 -68-47	1.2 17.2 -68-47
Site D	5.2 11.9 -46-70	4.6 13.8 -68-73	3.8 15.3 -60-67	2.6 14.9 -49-71	2.6 17.2 -69-68	20.7 18.6 -68-73	0.1 18.3 -69-69
Site E	3.2 11.8	3.0 13.0	2.8 14.8	2.5 17.0	2.0 19.5	2.0 19.5	1.5 20.3

	-47-60	-60-56	-49-67	-60-56	-68-57	-68-57	-71-60
Site F	3.7 11.1 -67-63	3.6 12.1 -71-76	3.7 13.6 -67-56	3.2 14.5 -67-56	2.1 15.4 -67-81	1.9 16.1 -67-79	1.1 16.7 -69-80
Site G **(Converted LogMar Score)**	2.6 9.2 -15-20	-2.6 5.2 -15-10	-10.1 15.5 -45-0	-6.4 10.6 -30-5	-2.0 10.9 -16-22	-1.9 7.5 -15-10	-10.5 18.3 -45-10

Table 8: VA Change in Letterscore by Site

3.7.2 Injector Profession and Injected Drug

There was a total of 203,271 injections recorded by profession of injector in the dataset. Of the injections given, the majority (67%) were given by doctors, followed by nurses (28%). Optometrists gave the least number of injections (1%) (See Table 9 for further information). At all of the sites, the most common injector profession was a doctor. There was no missing data for this variable. There were 204,150 recorded by injected drug in the dataset (see Table 9 and for further information). The most frequently injected drug was Lucentis (64%) and the least frequently injected drug was Avastin (2%). Only one site (site D) used Eylea most frequently. All of the other sites used Lucentis most frequently.

	Injector Profession				Injected Drug		
Site ID	**Doctor (%)**	**Nurse (%)**	**Assistant Practitioner (%)**	**Optometrist (%)**	**Ranabizumab (%)**	**Aflibercept (%)**	**Bevacizumab (%)**
A	9068 (68.8)	3766 (27.8)	365 (2.7)	0 (0)	9553 (70.6)	3,959 (29.2)	29 (0.2)
B	31,552 (87.1)	4,495 (12.4)	0 (0)	2 (0.0)	25,051 (69.4)	10,891 (30.2)	138 (0.4)
C	17,749 (57.2)	7,061 (22.8)	3,132 (10.10)	0 (0)	21,243 (68.1)	9,932 (31.9)	13 (0.0)
D	23,516 (72.4)	5704 (17.6)	3,147 (9.7)	143 (0.44)	14,369 (42.7)	19,066 (56.6)	244 (0.7)
E	10,872 (54.5)	3,583 (18.0)	3,053 (15.3)	9,954 (49.9)	13,930 (70.2)	3,964 (20.0)	1959 (9.9)
F	41,109 (58.7)	28,012 (40.0)	256 (0.4)	598 (0.9)	45,432 (65.1)	24,184 (34.67)	153 (0.2)
G	14,703 (67.0)	6413 (29.2)	35 (0.2)	1 (0.0)	15907 (72.7)	3,772 (17.2)	2,060 (9.4)
All Sites	149,883 (66.6)	63,700(28.3)	9988 (4.4)	1633 (0.7)	129,618 (63.5)	71,996 (35.3)	2,536 (1.2)

Table 9: Injector Profession and Injected Drug by Site

3.8 Regression models

3.8.1 IMD Score on Letterscore and LogMar

The results are presented in Table 10. Controlling for bilaterality, ethnicity and smoking status, higher IMD scores appeared to be associated with lower letterscores and lower LogMar over 36 months; although they were not statistically significant in the models.

Variable	Coefficient	95% CI	Overall *P* Value
Letter scores (14,093 eyes and 12,623 patients)			
Constant	80.81	56.03, 105.59	<0.01
IMD Score	-0.6	-0.16, 0.03	0.21
Bilaterality*	-4.81	-8.10, 1.53	<0.00
Ethnicity**	-16.51	-39.73, 6.70	0.13
Smoking	-0.74	-2.85, 1.38	0.49
LogMar (14,093 eyes and 10,688 patients)			
Constant	78.50	52.81, 104.14	<0.01
IMD Score	-0.13	-1.33, -0.10	0.20
Bilaterality*	-1.82	-4.64, -1.00	0.20
Ethnicity**	-17.23	-41.61, 7.12	0.16
Smoking	-0.71	-2.74, 1.23	0.45

***Bilaterality= having two eyes in the study**

****Being non-white**

Table 10: Multiple regression output for IMD score effect on letterscore and LogMAR, controlling for bilaterality, ethnicity and smoking

3.8.2 IMD Score and Number of Injections

The results are presented in Table 12. Higher IMD scores were not associated with the number of injections received. There were 11,823 eyes and 10,688 patients.

Variable	Coefficient	95% CI	*P* Value
Constant	62.65	56.21, 69.08	<0.01
IMD Score	-0.07	-0.1.5, -0.01	0.08
Bilaterality*	-4.62	-0.36, -1.95	<0.01
Smoking	-0.14	-0.18,1.80	0.87
Ethnicity**	0.04	-0.36, 0.29	<0.01

***Bilaterality= having two eyes in the study**

****Ethnicity=being non-white**

Table 11: Poisson regression output for IMD score effect on number of injections, controlling for bilaterality, ethnicity and smoking

3.8.3 Variation in Site ID and Treatment Compliance

It can be seen from Figures 17 and 18, and Table 12 that across all sites the majority of patients received 3 injections at the three-month time-point. Site C had the highest compliance to treatment recommendations (92%) and Site B had the lowest (79%). Figure 16 and Table 12 show a very different picture at the one-year time-point, however. They show that all sites had a majority of patients that did not receive at least 8 anti-VEGF injections at the year one time-point. Site C again had the highest compliance to treatment recommendations (33%) at the one-year point, and Site B again had the lowest (21%). This could be indicative of adherence or service delivery and included the discontinuation frequency.It could also be indicative of the sites' injection protocol. For example, some sites may be using fixed dosing protocols.

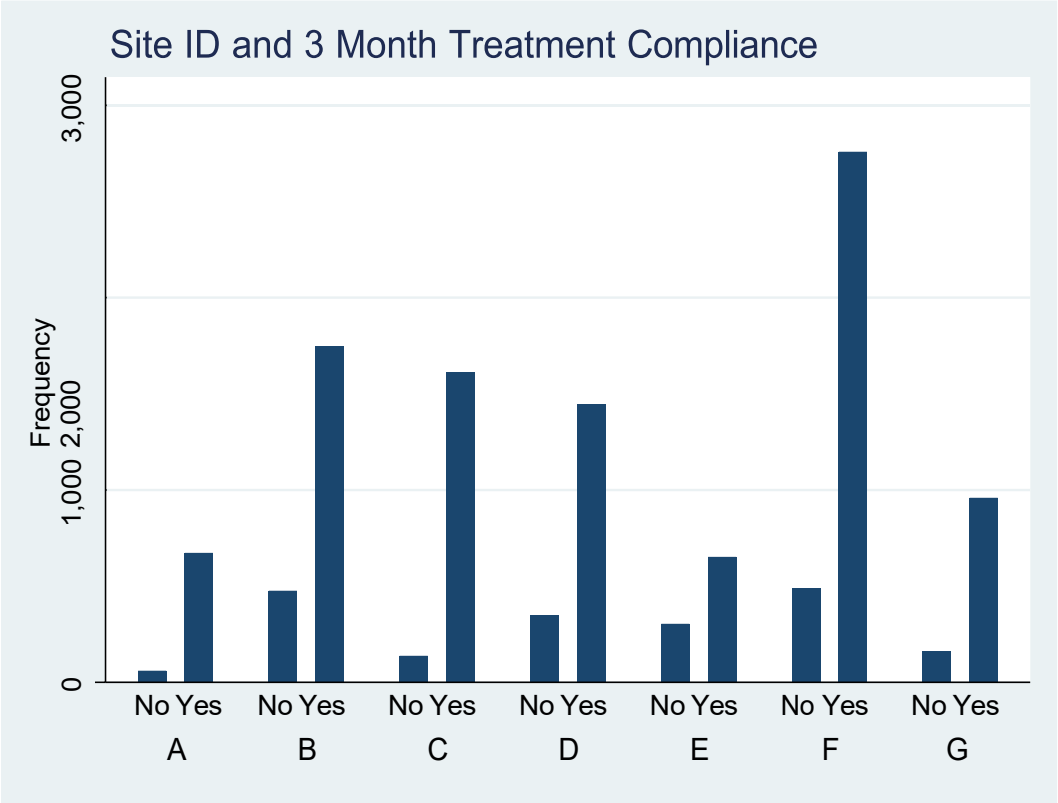

Figure 17: Site ID and 3 Month Treatment Compliance

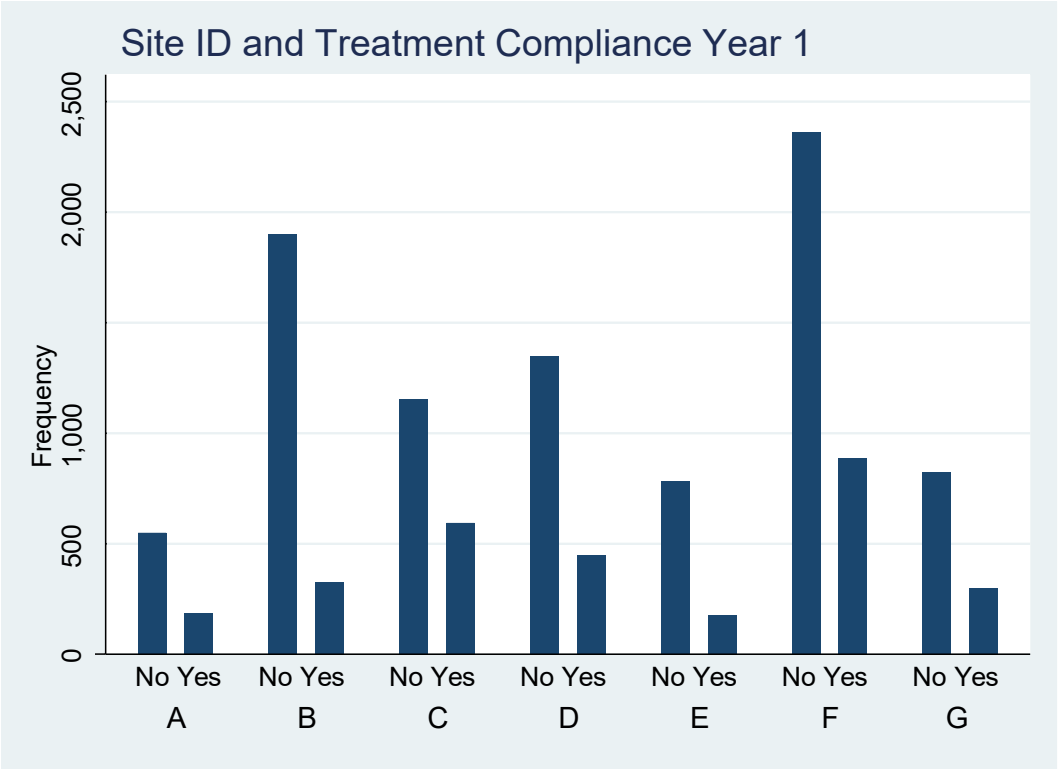

Figure 18: Site ID and 1 Year Treatment Compliance

Site ID and 3 Month Treatment Compliance Compliance				Site ID and 1 Year Treatment Compliance		
Site ID	**No (%)**	**Yes (%)**	**Total**	**No (%)**	**Yes (%)**	**Total**
A	60 (8.2)	672 (91.7)	733	549 (74.9)	184 (25.1)	733
B	476 (21.4)	1,747 (78.6)	2,223	1,899 (85.4)	324(14.6)	2,223
C	138 (7.9)	1,610 (92.1)	1,748	1,154 (64.7)	594 (33.3)	1,784
D	350 (19.5)	1,445 (80.5)	1,795	1,348 (75.1)	447 (25.0)	1,795
E	304 (31.8)	652 (68.2)	956	781 (81.7)	175 (18.3)	956
F	490 (15.1)	2,758 (84.9)	3,248	2,362 (72.7)	886 (27.3)	3,248
G	162 (14.5)	959 (85.5)	1,121	824 (73.5)	297 (26.5)	1,121

Table 12: Site ID and three month and one year treatment compliance rates

There were 11,823 eyes and 9553 patients at both 3 and 12 months. The results are presented in Table 13. IMD scores appeared to be associated with compliance with recommended treatment levels at 3 months and 12 months in this study sample, but the odds ratios (OR=0.99) were so small this does not translate into a meaningful finding.

Month 3				12 Months		
Variable	**Odds Ratio**	**95% CI**	***P* Value**	**Odds Ratio**	**95% CI**	***P* Value**
Constant	6.22	2.31, 16.80	<0.01	0.25	0.23, 0.43	<0.01
IMD Score	0.99	0.98, 1.10	<0.01	0.99	0.99, 0.10	<0.01
Bilaterality*	1.82	1.35, 2.44	<0.01	1.30	1.12, 1.52	<0.01

Smoking	0.88	0.76, 1.02	0.09	0.92	0.82, 1.02	0.09
Ethnicity**	0.94	0.42, 2.10	0.87	1.23	0.42, 2.10	0.87

***Bilaterality= having two eyes in the study**

****Ethnicity=being non-white**

Table 13: OR output for IMD score effect on compliance with recommended number of injections at 3 and 12 months, controlling for bilaterality, ethnicity and smoking at all sites

3.8.4 IMD Decile and Bilateral nAMD

Figure 19 and Table 14 show that in all IMD deciles, there were more patients with one eye impacted in the study rather than both. The IMD decile with the greatest proportion of bilateral patients was decile one (21%). The IMD decile with the lowest proportion of bilateral patients was decile 4 (17%). Controlling for ethnicity and smoking status, over 36 months IMD decile was not associated with developing nAMD in both eyes (see Table 15 for further information).

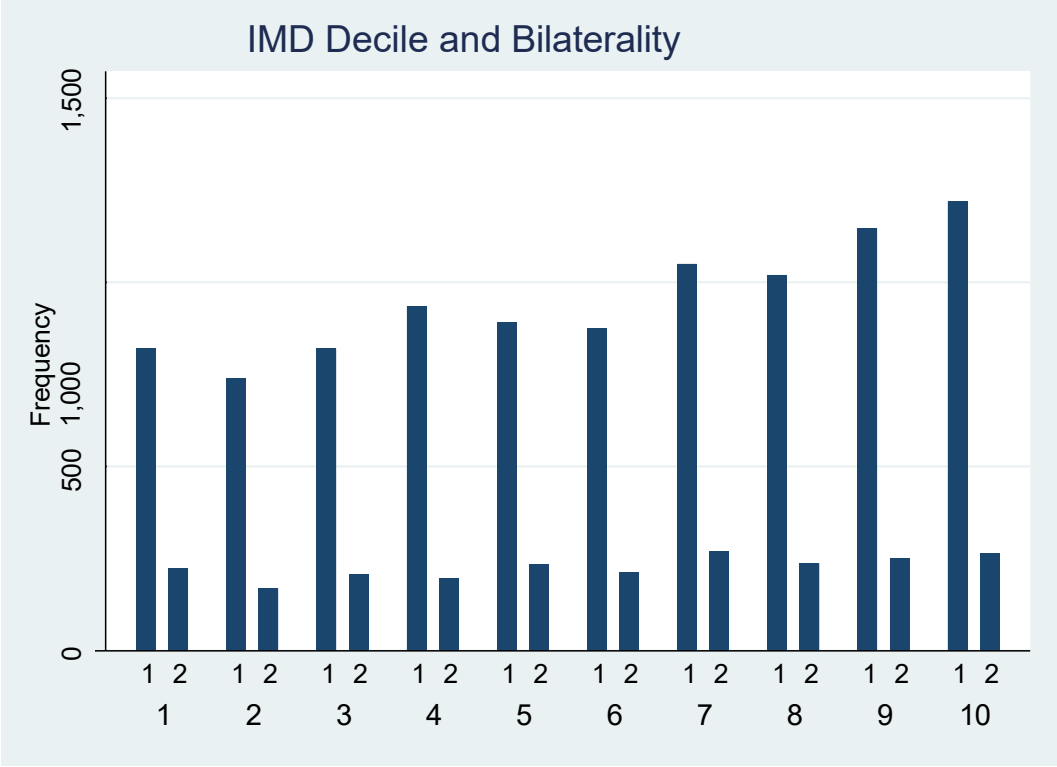

Figure 19: Bar Chart of IMD Decile and Bilaterality (1= 1 eye in study, 2=2 eyes in the study. 1-10 represents IMD Deciles) at all Sites

IMD Decile and Bilaterality			
IMD Decile	**Single Eye in Study (%)**	**Two Eyes in Study (%)**	**Total**
1	821 (78.6)	224 (21.4)	1,045
2	739 (81.5)	168 (18.5)	907
3	820 (79.9)	206 (20.1)	1,026
4	935 (82.7)	196 (17.3)	1,131
5	891 (79.2)	234 (20.8)	1,125
6	875 (80.4)	213 (19.6)	1,088
7	1,050 (79.5)	270 (20.5)	1,320
8	1,020 (81.1)	237 (18.9)	1,257
9	1,146 (82.1)	250 (17.9)	1,396
10	1,219 (82.2)	264 (17.8)	1,483

Table 14: IMD Decile and Bilaterality at All Sites

Variable	Coefficient	95% CI	*P* Value
Constant*	1.3	1.2, 1.4	<0.01
IMD Decile	-0.0	-0.0, 0.0	0.97
Smoking	-0.0	-0.0, 0.0	0.1
Ethnicity**	-0.1	-0.0, 0.03	0.1

***Bilaterality= having two eyes in the study**

****Ethnicity=being non-white**

Table 15: Logistic regression output for IMD decile and bilaterality for all sites controlling for smoking and ethnicity

3.8.5 Association between Smoking Status and Visual Loss at All Sites

There was no evidence of an association found in this study between smoking and visual loss of >15 letters at 36 months (see Tables 16 and 17 for further information).

Variable	Odds Ratio	95% CI	Overall *P* Value
Constant	-0.4	-8.5, 239.0	0.00
IMD Score	1.0	0.1, 1.0	0.33
Bilaterality*	0.5	0.3, 0.7	<0.00
Smoking	1.1	0.8, 1.3	1.3
Ethnicity**	0.9	0.2, 3.9	0.92

***Bilaterality= having two eyes in the study**

****Being non-white**

Table 16: Odds ratio output for smoking status effect on visual loss of >15 letters, controlling for bilaterality, ethnicity and smoking at all sites

Visual Loss of >15 Letters				Visual Loss of <15 Letters		
Time-Point	**Current Smoker/Ex-Smoker (%)**	**Never Smoked**	**Total**	**Current Smoker/Ex-Smoker (%)**	**Never Smoked**	**Total**
3 Months	29 (25.9)	83 (74.1)	112	1635 (31.4)	3,570 (68.6)	5,205
6 Months	43 (28.1)	110 (71.9)	153	1649 (31.9)	3,543 (68.1)	5,164
12 Months	70 (33.5)	139 (66.5)	209	1594 (31.2)	3,514 (68.8)	5,108
18 Months	79 (35.0)	147 (64.5)	226	79 (32.5)	157 (67.5)	243
24 Months	87 (35.8)	156 (64.2)	243	1577 (31.2)	3,497 (68.8)	5,074
30 Months	86 (35.4)	157 (66.6)	243	1578 (31.1)	3,496 (68.9)	5,074
36 Months	72 (31.6)	156 (68.4)	228	1592 (29.9)	3,653 (70.1)	5,317

Table 17: Smoking status and visual loss at all sites

3.9 Discussion

The overall aim of this analysis was to explain variation in both visual outcomes and number of injections received across seven NHS ophthalmology departments. This study is one of a number of UK studies that have used EMR data to look at a wide variety of causes of variation in visual outcome in patients with nAMD being treated with anti-VEGF therapy, and variation in treatment delivery. This is an important issue because the ability to explain as much variation in visual outcome as possible could enable clinicians to better target treatment regimens and could therefore improve visual outcomes in nAMD generally. It is also important to be able to explain variation from a real-world dataset such as the one used in this study, because clinical practice often fails to replicate the levels of treatment from clinical trials.

There were 14,093 eyes in the study at baseline, and 2,772 at the final time-point of 36 months. The visual outcome pattern of an initial three-month spike in visual acuity, followed by a gradual decline was seen in most patients, which concurs with findings by other relevant recent studies (Cheema *et al.,* 2021; Spooner *et al.,* 2021; Phan *et al.,* 2021 and Li *et al.,* 2021). The reasons for loss of patients at 36 months could not be clearly identified in this study. One reason for this attrition is likely to be in part due to death, as the patients in this study were of an older age. However, it did appear that those with lower starting VA at baseline and older age were less likely to still be receiving treatment at 36 months. Older adults not receiving treatment at 36 months could be largely due to other health conditions and/or problems with transport preventing them from getting to clinic for regular monitoring and treatment. Patients who had lower baseline VA were also less likely to receive the recommended treatment in year one (Hamilton *et al.,* 2020.

In this study, the regression models used did not find an association between higher social deprivation and lower visual outcomes. Although they were not statistically significant, the models suggest that those with higher levels of social deprivation had worse visual outcomes. However, data from a UK cohort study looking at social deprivation and being classed as having low vision due to a range of causes that found that people who were classed as low vision were more likely to live in socially deprived areas (Yip *et al.,* 2015). It is also acknowledged that as this dataset spans a number of years of people being treated, clinical guidelines have changed regarding treatment patterns and the involvement of allied health care professions in

monitoring and treatment. This could have also impacted on the number of injections patients in this study received. However, even in those eyes that were still being treated at 36 months, the initial gains made at 3 months did fall at each time-point, appearing to show initial gains were unable to be maintained long-term. This suggests that there is a physiological rather than social or service-related cause for this, which is outside of the scope of this study to identify.

However, social deprivation itself did not explain variation in numbers of injections, and this is similar in other studies showing that patients with better baseline VA tend to receive more injections. This points back to the findings of this study and other current literature described above, that social deprivation does have a small effect on visual outcome, and number of injections received is more a product of low VA.

This study was also unable to show that smoking status explained variation in visual loss at 36 months. A recent study in Australia investigated the relationship between smoking and visual outcomes agreed with the findings in this study, where it found that although being a current smoker led to a lower age of developing nAMD, visual outcome was not significantly affected at 12 months (Deteram *et al.,* 2019). In addition, another large systematic review found no evidence of smoking having an effect on visual outcome (Phan *et al.,* 2021).

This study was unable to analyse any other social behaviours or health conditions, such as diabetes or heart disease, because of a lack of reliable reporting on this in the dataset, a fact that is consistent with general problems of working with real-world data. It also reflects the inability to do this in the systematic review carried out in Chapter 2 of this thesis.

3.9.1 Limitations

This study did have some important limitations. The first of these is the fall in numbers of eyes from baseline to 36 months; however other studies in this field using real- world data also share this limitation (Calvo *et al*, 2015; Razi *et al.,*2016). The study population was strongly primarily white, and in order to meaningfully be able to include ethnicity in the models, ethnicity had to be divided between white and non-white. It is recognised that this was a crude approach and may have not been able to detect differences between each ethnic group. This study was also unable to analyse the

impact of other health conditions, such as heart disease or diabetes, because there was too much inconsistency in reporting of past medical history in the dataset to carry out meaningful analyses.

Despite the fact that real-world data better reflects the challenges of treatment delivery and adherence, along with real-world visual outcomes, it does have its' disadvantages. One of the most prominent of these being the need to spend significant time cleaning often very messy real-world datasets, due to the fact that data are often recorded differently between clinicians and hospital sites, with little standardisation. For example, one site recorded no data at all on ethnicity of their patients. With sites that did record data on ethnicity, several descriptions of the same ethnicity were used freely, making cleaning and analysis increasingly difficult. Due to the inconsistency of data reporting and need to effectively merge data files, whilst adhering to exclusion criteria without dropping observations unnecessarily, data cleaning took over two years. This took up an unanticipated time of the study period, and limited what could be done with the data in terms of analysis, even with the support of two statisticians. This process highlighted the practical difficulties of working with real-world data.

3.9.2 Future research areas to be explored

There are further questions to be answered in this field. These include:

Do patients with higher levels of social deprivation get diagnosed later or have more difficulty accessing services (for example regular optician checks)? If so, how could this be addressed?

As social deprivation did not explain variation in number of injections received and compliance with the recommended number of treatments, what other factors explain this? Is it more likely that it is issues with services being able to deliver enough injections, or is it more that there is something inherent about patients that are less compliant with treatment? For example, in those patients that are less compliant, are they older and have less access to transport to hospital? Or is it a reflection of general compliance with healthcare interventions generally? Or instead of focusing on the number of injections, it could be more effective to look at how there can be closer monitoring and personalisation of treatment, such as in individual treatment patterns that are delivered.

If there had been better information on ethnicity, and more sites with more variation in the ethnic background of patients, would there have been more variation in visual outcome? Would it be possible to identify whether certain ethnicities had particularly better or worse outcomes? If so, work needs to be done on addressing any inequalities.

How does visual outcome affect quality of life? Do patients with declining visual loss over time report declining quality of life, or would any decline in quality of life be caused more by general aging and other associated health conditions?

3.9.3 Conclusions

Social deprivation was not found to have an impact on visual outcomes in the patients in this study over 36 months. Social deprivation did not influence the number of injections received or whether the optimum treatment level was achieved in year 1. Neither did smoking have any influence on whether patients lost more than 15 letters. However, the potential association between increased social deprivation and poorer outcomes is an important finding, as it sits within a bigger picture of inequalities across healthcare access and outcomes and raises questions about whether patients with higher social deprivation are being diagnosed later for nAMD, and therefore having poorer visual outcomes as a result. Now that it has been established that there is variation in visual outcomes nationally in patients with nAMD being treated with anti- VEGF therapy, it is important to establish how this is related to self-reported quality of life. No data on this was available in the retrospective dataset. Therefore, in the next chapter, this will be investigated in a smaller cohort of patients at a teaching hospital in York, using regression models. This will enable an attempt to discover how variation in visual outcomes and the effect of age at diagnosis, as found in Chapter 3, is linked to quality-of-life outcomes.

4.0 Variations in Visual Outcomes and Self-Reported Quality of Life in Patients with Neovascular Macular Degeneration at a UK Teaching Hospital: A Prospective Cohort Analysis

4.1 Introduction

As discussed in Chapters 2 and 3, it has been found that not only that age at baseline, number of injections and visual acuity at baseline contribute to the success of anti- VEGF treatment for nAMD, but that there is significant variation in visual outcomes. However, what is still unknown is how this variation relates to self-reported quality of life in these patients. This chapter therefore explores this in a small cohort of patients recruited from a teaching hospital in North Yorkshire. The population that this hospital was served by was a relatively affluent and rural city or village dwellers and a largely white population.

4.2 Aims

This cohort study described variation in visual outcome and quality of life at a teaching hospital in North Yorkshire. The data were collected prospectively. This study aims to:

i) Descriptively present the characteristics of the population under study.

ii) Explore changes in visual outcomes and patient reported quality of life outcomes over 12 months

iii) Explore if health-related quality of life (using both a generic and disease specific quality of life measure) is associated with changes in visual acuity outcomes

4.3 Background to quality of life and ageing

Literature suggests that as people age, even without significant visual loss, their quality of life tends to decline over time (Vorst *et al.,* 2017; National Academies of Science *et al.,* 2016; Netuveli *et al.,* 2006). A study of quality of life and ageing reported autonomy, activity, health perception, relationships, attitude and adaptation, emotional comfort, spirituality, home and neighbourhood, and financial security as some of the most important domains of quality of life in older adults (Leeuwen *et al.,* 2019). However, it has been argued that it is not ageing itself that determines a steady decline in reported quality of life, but the domains reported above, particularly family and friend relationships, financial status and the ability for adaptation being particularly important (Leeuwen *et al.,* 2019; Netuveli and Blane, 2008). The effect of

these domains has been exacerbated since the introduction of lockdowns during the COVID-19 epidemic (Duan *et al.,* 2021).

This prospective study is important, because being able to measure patient reported quality of life alongside visual acuity outcomes, gives a better picture of overall quality of care. For example, could patients reporting lower quality of life, even if this isn't reflected in visual acuity outcomes, need referral to other services, such as occupational services, more regular reviews, or volunteer services or community teams that could support the individual? Although chapters two and three of this thesis explored reasons for variations in visual outcome, it is also important to understand variations in self-perceived quality of life alongside this, as it seems important to argue that quality of life is also an important measurable outcome that could reflect on quality of services. This prospective study is therefore being carried out in order to begin to understand this link. It will allow the ability to track both the progression of patients' visual acuity, alongside corresponding changes in self-reported quality of life. Do they follow the same progression trajectory? Even though, as highlighted in the descriptive statistics in Chapter 3, visual acuity does tend to decrease over time, and as in the above paragraph in this chapter, self-reported quality of life does tend to decrease with ageing even without visual loss, however, do they both decrease at a similar rate?

4.4 Methods

4.4.1 Ethical Approval Process

HRA approval was required, as this was a prospective study with patients, collecting anonymised patient data. Before being submitted to the HRA, it was initially reviewed by a research governance committee in the Department of Health Sciences at the University of York, as this study was undertaken as part of a PhD. Ethical approval for the study was granted in December 2018.

4.4.2 Recruitment of Participants

Patients were recruited from nAMD clinics at a teaching hospital in North Yorkshire. Patients were invited to take part in the study either by the author of this thesis, or a research nurse at site (as this study was adopted onto the National Institute of Health Research (NIHR) Portfolio of clinical research studies). Potential participants were given verbal and written information about the study and given extra time to consider their participation, if required. Each participant signed a consent form or had this completed or witnessed by an advocate if sight loss made this impossible. It was known who to approach from patient notes. Each patient was given an information sheet, and supported to complete a written consent form if willing to participate. There were only two patients not willing to take part, due to health issues. Data was collected through a combination of questionnaires and data from patient notes.

4.4.3 Data Management

The data were originally stored and analysed on a University PC within York Trials Unit at the University of York. The data itself were stored on a university drive, with access only granted to the investigator and the supervisory team. However, after the outbreak of COVID-19 in March 2020, the author of this thesis worked remotely. Data was then managed remotely through a virtual private network (VPN) from home on a laptop with restricted access, with double password protection. Permission from the NIHR was granted for this.

4.5 Data Management

Despite the majority of data being collected by the author of this thesis, there was still some missing data. This was due to unavailability of notes, patient death, or general loss to follow-up. This resulted in 59 patients of the 117 recruited being lost to follow up.

4.5.1 Exclusion criteria

Eyes with concomitant central retinal vein occlusion (CRVO), brachial retinal vein occlusion (BRVO), traumatic eye injury and cataract surgery within 3 months were excluded from the analysis. The reasons for this are detailed in Table 18.

Exclusion Criteria	Reason
CRVO diagnosis	Eye may already be being treated with anti-VEGF for CRVO, so impossible to attribute any visual effects purely to treatment for nAMD.

BRVO diagnosis	Eye may already be being treated with anti-VEGF for CRVO, so impossible to

	attribute any visual effects purely to treatment for nAMD.
Traumatic eye injury	Eye injury could lead to decreased visual acuity that makes it difficult to understand the effects of anti-VEGF therapy for nAMD.
Cataract surgery within 3 months	Recent cataract surgery can lead to increased visual acuity, so would be impossible to tell if any changes in visual acuity were due to the cataract surgery or anti-VEGF treatment for nAMD.

Table 18: Reasons for exclusion criteria

4.5.2 Better seeing eyes in patients with bilateral nAMD

It was decided *a priori* that where a patient in the study had bilateral nAMD, to only include their better seeing eye. Although there are studies that argue that the better seeing eye is most strongly associated with quality-of-life outcomes, there are also studies that showed the worse eye had a stronger association and those that argued that both worse and better seeing eye equally affected quality of life outcomes (Elshout *et al.,* 2017; Nickels *et al.,* 2019; Zhu *et al.,* 2017). However, the decision was made to use best seeing- eye in the bilateral patients in this study, as it was felt to be the better predictor of patient reported quality of life, as vision in this eye tends to compensate somewhat for the weaker eye.

4.5.3 Data collection

Information was collected on:

- EQ5D-5L

- NEI VFQ-25
- Age
- Gender
- Study eye/s
- ETDRS score
- VA method
- Number of visits
- Number of treatments in each eye/s
- Treatment drug
- Date of first treatment

4.5.4 EQ-5D-5L Tool

The EQ-5D-5L is a generic quality of life tool including dimensions on mobility, self- care, usual activities, pain/discomfort and anxiety/depression with a visual scale for individuals to indicate how good or bad their health is today on a 0 to 100 scale.

The EQ-5D-5L tool has been widely used as a patient reported outcome in clinical services, and in both economic and non-economic research (Brazier *et al.,* 2019; Wang *et al.,* 2021). The advantages of using the EQ-5D-5L tool include its ability to be used on a wide-range of health conditions, and to generate an index value, that can be adjusted depending on country of administration (Jain *et al.,* 2020). However, the tool is less effective in assessing patient reported quality of life for specific health conditions and has also received criticism of unresponsiveness and ceiling effect, and instrument sensitivity and to reduce ceiling effect were some of the reasons it was extended to a five-point response to each question for the original 3-point response (Nolan *et al.,* 2016).

4.5.5 NEI VFQ-25 tool

The National Eye Institute Visual Functional Questionnaire (NEI VFQ-25) includes 25 vision targeting questions representing 11 vision related constructs plus a single item general health rating item. It focuses on global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and colour vision.

The NEI VFQ-25 has been found to be responsive to changes in vision-related quality of life, and in helping to predict advancing nAMD (Lindblad and Clemons, 2005; Sivaprasad *et al.* 2018; Jelin *et al.,* 2019). However, its ability to do this has been found to be limited when not used alongside traditional visual measurement techniques (Owen *et al.,* 2006).

4.5.6 Sample size and statistical analysis

Due to the observational nature of this study, no formal power calculation was undertaken but it was aimed to recruit 250 patients. However, due to the COVID-19 pandemic, which led to many potential patients shielding, only 117 patients were recruited to the study, and only 58 patients had useable data at both baseline and 12 months. Linear regression models were developed using utility scores for EQ-5D-5L and total NEI VF-25Q score as the outcome and visual acuity as the independent variable, controlling for number of visits, injections and age. As Chapter 2 has shown, both from the literature and the systematic review in this thesis, number of visits had a highly significant impact on visual acuity.

4.5.7 Cleaning and Merging

The files were received as Excel spreadsheets. Each was imported into Stata version 16. Each variable was reformatted where necessary for ease of use, for example changing date formats from string to date format. Once this was done, the process of merging all of the relevant files were undertaken. Patients with no data were excluded from the analysis.

4.6 Results

The data were collected during July 2021. The cleaning process took place between August 2021 and October 2021. There were 117 patients who had complete data at baseline and 58 patients who had complete data at 12 months. Of the 59 patients lost to follow-up, 7 had died, 3 withdrew from the study, it was not possible to retrieve clinical notes for 1 patient, and the remaining 50 patients were uncontactable by telephone, as face-to-face follow-up was not feasible due to COVID-19.

4.6.1 Characteristics of the population under study

The characteristics of the study population are presented in Table 20. Of the patients included in the study, 27 (50%) had two eyes being treated for nAMD (although as described in section 4.5.2 of this chapter, only the best seeing-eye was included in the analyses). Just over two-thirds of the sample were female (n=66) and the median age was 84 with the youngest patient being 55 and oldest 97 (Figure 20).

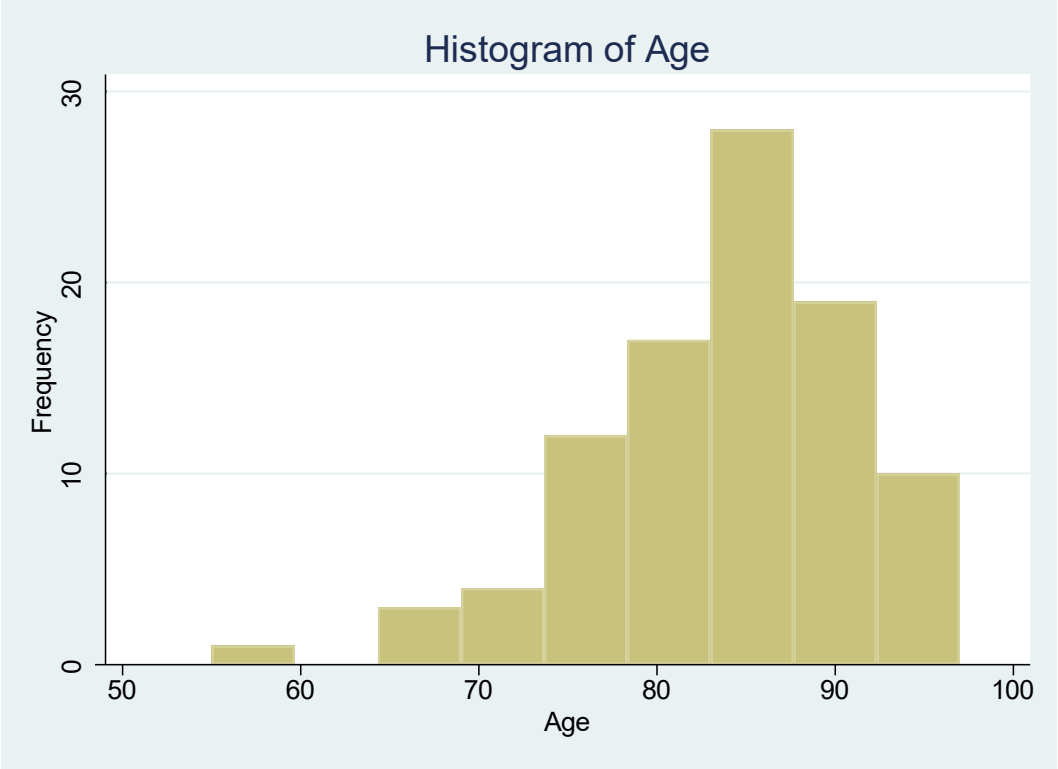

Figure 20: Histogram of age at baseline

4.6.2 Changes in visual outcomes over 12 months

There were 58 observations with ETDRS scores and quality of life follow-up at 12 months. The median baseline ETDRS score was 70 (min 0 and max 85) and only dropped slightly at 12 months to 69 (min 6 and max 85). The median number of clinic visits increased from 27.5 (min 4 and max 138) at baseline to 37.5 (min 6 to max 124) at 12 months. The median number of injections patients received at baseline was
15.5 (min 0 and max 121) and this increased at 12 months to 22.6 (min 0 and max 120). Across all participants, only glasses or unaided were the VA method used. At both baseline and 12 months, glasses were the most common method, 79 and 74% respectively). The mean VA change was -4.1(SD 20.1) (see Table 19 and Figures 21, 22 and 23 for further information). However, there was a wide range of VA change, ranging from a loss of more than 70 to a gain of more than 60.

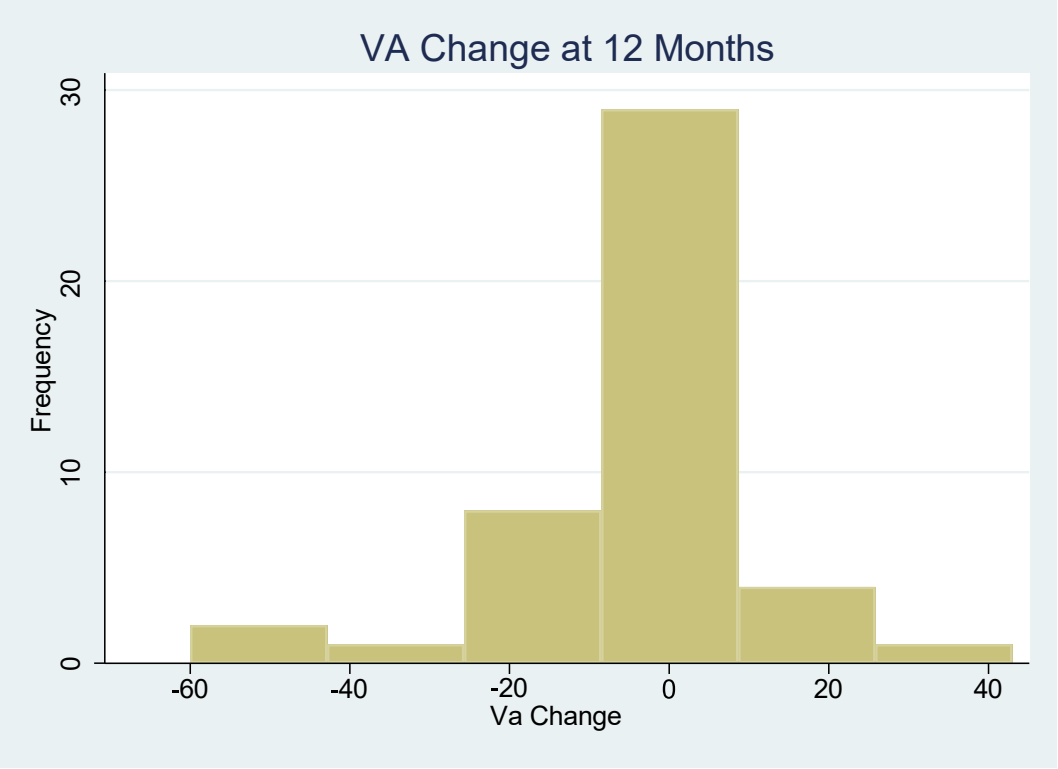

Figure 21: Histogram of VA change at 12 months

	Baseline					12-Months				
	Number (%)					Number (%)				
Male	33 (32.4)					31 (27.2)				
Female	66 (64.7)					77 (67.5)				
	Mean	**Median**	**Standard Deviation**	**Interquartile Range**	**Range**	**Mean**	**Median**	**Standard Deviation**	**Interquartile Range**	**Range**
Age	83.4	84	7.5	68 – 95	55 – 97	83.3	84	7.2	68 – 84	54 - 87
ETDRS Score	65.1	70.0	16.0	26 – 84	0 - 85	60.1	69	19.5	27 – 83	6 - 85
Number of Visits	38.6	27.5	29.4	5 – 102	4 – 138	47.6	37.5	32.2	14 – 114	6 – 124
Number of Injections	22.4	15.5	20.0	4 – 61	0 – 121	27.9	21.5	22.6	0 – 62	0 – 120
Visual Loss						4.4	4.0	20.1	-15 – 41	-71 - 64

Table 19: Summary statistics of gender, age, visual acuity, number of visits, number of injections and visual loss

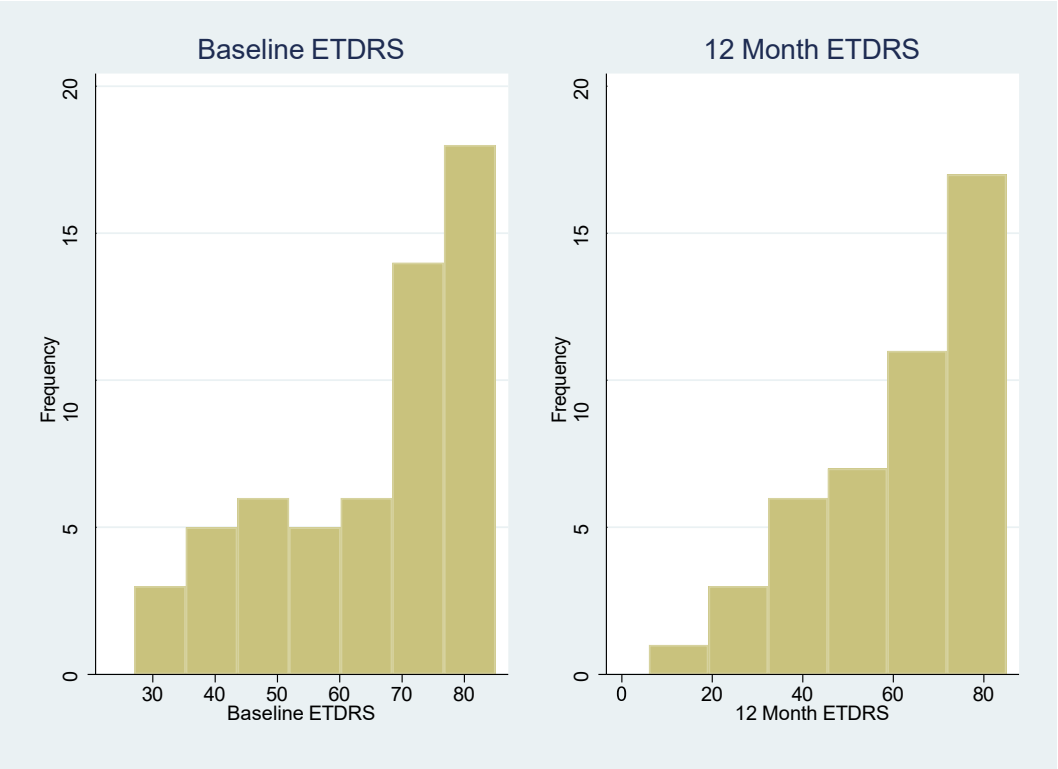

Figure 22: Baseline and 12-month ETDRS scores

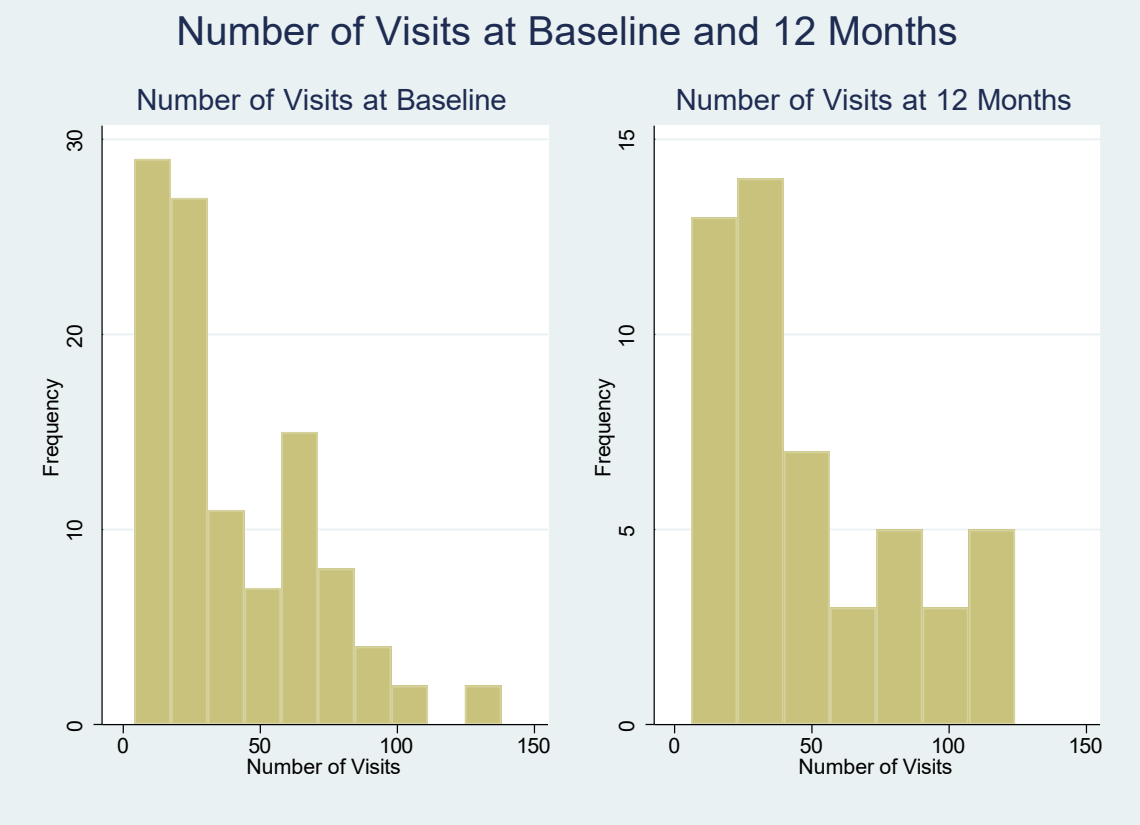

Figure 23: Histogram of number of visits at baseline and 12 months

4.6.3 Changes in quality-of-life outcomes over 12 months

The mean overall utility score for the EQ-5D-5L was 0.8 at baseline, and 0.7 at 12 months, representing a decline. Between baseline and 12-months, in the domains of mobility, self-care, activities and pain, patients reported a decrease in problems (see Tables 20 and 21 for further information). However, for anxiety and overall self- reported vision, reported problems were increased at 12 months. At 12 months, in every domain except overall self-reported vision, the majority of patients reported the same level of problems in each domain. At baseline the mean VAS EQ5D-5L score was 73 (SD 21.8), and at 12 months it reduced with a mean of 70 (SD 1.2). The highest possible EQ5D-5L profile was 11111, and the lowest was 55555. This is significant because it shows that the full range of possible scores were represented. However, it was not statistically significant. At baseline, 31 patients (26.5%) had the highest possible overall EQ5D-5L profile, and no patients had the lowest (0.0%). At 12 months, 13 patients (23.6%) had the best possible EQ5D-5L profile, and no patients had the worst (0.0%). These were patients that had a good starting and final VA.

Level	Mobility		Self-Care		Usual activities		Pain/Discomfort		Anxiety/Depression	
	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
0	2 (1.7%)	34 (58.6%)	0 (1.7%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
1	55 (47%)	10 (17.2%)	96 (82%)	56 (94.9%)	65 (55.6%)	40 (70.0%)	61 (52.1%)	32 (55.2%)	71 (60.7%)	34 (58.6%)
2	27 (23%)	6 (10.3%)	9 (7.7%)	0 (0.0%)	22 (18.8%)	6 (10.3%)	27 (20.7%)	12 (20.3%)	34 (29.1%)	11 (19.0%)
3	17 (14.5%)	6 (10.3%)	5 (4.3%)	1 (1.7%)	15 (12.8%)	7 (12.1%)	19 (16.2%)	12 (20.3%)	7 (6.0%)	7 (12.1%)
4	12 (10.3%)	8 (13.8%)	1 (1.0%)	0 (0.0%)	7 (6.0%)	2 (3.4%)	6 (5.1%)	3 (5.1%)	3 (2.6%)	3 (5.2%)
5	4 (3.4%)	1 (1.7%)	4 (3.4%)	2 (3.4%)	7 (6.0%)	3 (5.2%)	3 (2.6%)	0 (0.0%)	1 (0.9%)	4 (6.9%)
Total	117	58	115	58	117	58	117	58	117	58
Number reporting some problems* **	60 (51.3%)	58 (36.2%)	19 (16.5%)	3 (5.1%)	51 (43.6%)	18 (31.0%)	55 (47.0)	27 (45.8%)	45 (38.5%)	25 (43.1%)
Number of patients reporting worse outcomes[a]	14 (24.1%)		5 (8.6%)		9 (15.5%)		16 (27.6%)		18 (31.0%)	
Number of patients with the same outcomes[a]	30 (51.8%)		50 (86.2%)		33 (56.9%)		30 (51.7%)		29 (50.0%)	

Number of patients with better outcomes[a]	14 (24.1%)	3 (7.0%)	16 (23.6%)	12 (20.7%)	10 (29.0%)

Table 20: Distribution of mobility, self-care, activities, pain and anxiety domains at baseline and 12 months

*****Levels 2-5 which represent some problems**

[a]Results are for those w1ho completed both the baseline and 12-month questionnaires

Time-Point	Mean	Standard Deviation	Median	Range	Interquartile Range
Baseline	72.7	21.8	75	0 – 96	35 – 95
12 Months	70.0	21.3	70	8 – 99	30 - 98

Table 21: Descriptive statistics for visual analogue scale

At baseline the mean average score the NEI VF-25Q score was 55.1 and at 12 months this was slightly higher at 56.3 (see Table 22 for further information).

Time-Point	Mean	Standard Deviation	Median	Range	Interquartile Range
Baseline	55.1	9.0	57.3	31.9 – 70.0	37.5 – 66.7
12 Months	56.3	9.6	57.6	16.7 – 71.5	40.0 – 68.8

Table 22: Descriptive statistics for total average NEI VF-25Q scores at baseline and 12 months

4.6.4 Relationship between health-related quality of life and visual acuity

There was no evidence of an association between EQ_5D-5L or NEI VF-25Q and ETDRS at the end of the study period, when controlling for age, number of visits and number of injections (see Table 23 for further information). The confidence intervals found in this analysis remained at 0.00, which was an unexpected finding. However, this is likely to be due to the small sample size of this study. Despite the small size of this sample, in the EQ-5D-5L model age had the strongest statistical significance, whereas in the NEI VF-25Q model, this was number of injections.

Outcome	Predictor Variable	Regression Coefficient	Standard Error	95% CI	*P* Value

EQ-5D- 5L	ETDRS	0.0	0.0	-0.0, 0.0	0.4
	Age	-0.0	0.0	-0.0, 0.0	0.1
	Number of Injections	0.00	0.00	-0.00, 0.00	0.3
NEI VF-25Q	ETDRS	0.0	0.1	-0.2, 0.2	0.82
	Age	-0.2	0.4	-1.0, 0.6	0.68
	Number of Injections	-0.1	0.1	-0.4, 0.2	0.04

Table 23: Regression coefficients for EQ-5D-5L global index and NEI VF-25Q and visual acuity at 12 months, controlling for age, number of visits and number of injections

4.7 Discussion

Due to the COVID-19 pandemic that occurred during the time that this study was carried out, there was a much smaller sample size than anticipated which meant the conclusions that could be drawn were limited. Half of the patients in this study had bilateral nAMD. The majority of study participants were female, which fits with an established pattern of women generally living longer than men. Overall visual acuity declined over the 12-month study period (by 4 letters) which was consistent with current literature. Due to the smaller than hoped for sample size of this study, number of visits was described, but was unable to be meaningfully analysed.

In terms of the EQ-5D-5L, at baseline the best and worst domains were mobility and self-care; however, at 12 months the best domain was anxiety/depression. This suggests that having treatment does have a positive impact on anxiety/depression over time but does not have an impact on self-reported visual acuity. This could possibly be because of receiving treatment for nAMD. The majority of patients in this study self-reported a decline in visual function as part of the overall vision bolt-on element as used in this study, irrelevant of actual visual acuity, the

number of visits or injections. However, a quarter of patients reported the best possible self-reported EQ-5D-5L profile. With the NEI VF-25Q tool, at baseline the best and worst outcome domains were peripheral vision and driving respectively, but at 12 months peripheral vision was the best scoring domain and being dependent on others the worst domain outcome. This suggests that as time goes on, patients in this study became more dependent on others, and that this became more of a problem as nAMD progressed. However, the average total scores did rise at 12 months marginally.

There was no association found between the EQ-5D-5L nor NEI VFQ-25 scores and visual acuity.

The largest flaw in this prospective analysis has been the much smaller than expected sample size. It seems a fair assumption that the small sample size in this study has prevented any truly meaningful conclusions being made from this prospective study. The smaller than hoped for sample size was partly due to slower than anticipated recruitment, and the fact that the COVID-19 epidemic put the study on hold, and meant that many of the study patients were self-isolating. Any future studies in this area would need to recruit a much bigger sample size to produce more meaningful results. However, one interesting result of having to change to telephone follow-up rather than in-clinic follow-up was that on a practical level it worked a lot better, and patients were more than happy to be followed up by telephone, rather than in the environment of a busy clinic where they can be called in to be seen at any time. Any future studies in this area should consider recruiting from AMD clinics, but questionnaires completed over the telephone, where there are no time constraints.

Another consideration of the methodology of this prospective study was that in retrospect, the author of this thesis would have collected data on both eyes if the patient had unilateral nAMD. The evidence suggests that quality of life is better driven by the better seeing eye, and although this approach was taken in bilateral patients, VA outcome was analysed by the eye with nAMD in unilateral patients. The problem with this is that if the majority of patients are unilateral,and the non-AMD eye has better vision, it could lower VA relation to quality of life outcomes. In terms of future research in this area in general, being able to use binocular VA measurement may be helpful.

4.8 Conclusion

Due to a small sample size, it is difficult to make an assertion that self-reported quality of life is associated with visual acuity over time. However, it seems logical that a larger study would be feasible to explore this in the future, to get more definitive results. But this study did identify variations in quality of life and visual outcomes. In future it may also be more feasible to conduct questionnaires by telephone, for practical purposes.

5.0 Discussion

5.1 Introduction

The overall aims of this thesis were to:

- Determine which factors influence the effectiveness of anti-VEGF therapy for patients with nAMD.
- Investigate how much variation there is nationally in visual outcomes in patients with nAMD being treated with anti-VEGF therapy.
- Investigate if there is a relationship between visual outcomes and patient reported quality of life outcomes.

This discussion chapter aims to use the research presented in this thesis to discuss how each aim has been addressed and the conclusions that have been drawn from each. This chapter will seek to place the findings of this research into the wider context of variation in healthcare generally, as variation in outcomes is not a unique occurrence to ophthalmology. It will also scrutinise the methods used and how these could be strengthened in future work. This will be explained in the context of carrying out much of this research in the COVID-19 pandemic. It will also discuss future recommendations for research in this field.

5.2 Factors which influence the effectiveness of anti-VEGF therapy for patients with nAMD

This thesis was able to identify that age at baseline, number of injections received and visual acuity at baseline all influenced longer term visual outcome. Older age at baseline and lower baseline visual acuity had a strong tendency to result in poorer visual outcomes long-term, whereas a larger number of injections received was associated with better visual outcomes. However, this thesis was unable to find association between levels of social deprivation, smoking status (as in being a current or past smoker) and whether ethnicity (as in being non-white) had a significant impact on visual outcomes. This does not necessarily mean that there were not associations between smoking status, ethnicity and visual outcome, but that this thesis had insufficient data to find such associations. The identified factors highlight the

importance of early diagnosis and treatment, and how receiving the optimum number of treatments is important to improved long-term visual outcomes. The findings in this thesis of identified factors that affect treatment sit in line with the findings of the main clinical trials. However, using real-world data as a significant part of this thesis, has made exploring factors such as ethnicity and medical history difficult to meaningfully model, due to the incompleteness of much recorded data.

As established in this thesis, better visual acuity and lower age at baseline were strong indicators of better long-term visual acuity. This raises several important questions. Are there issues with delayed diagnosis and commencement of treatment? For example, is being diagnosed with nAMD at a later age or lower visual acuity associated with later diagnosis, possibly due to ethnicity or higher levels of social deprivation? Although this thesis was unable to detect this, it appears that future work should attempt to investigate this further. This is important, because if such issues are preventing timely diagnosis and treatment, if needed, this represents a failure of current service provision. For example, do people who experience higher levels of social deprivation engage more readily with high street optical services, therefore having their eyesight tested more regularly, with a higher probability of early onset of nAMD being more likely to be picked up? Although it was outside of the scope of this thesis to investigate this, it now seems relevant to this field of research, and something that needs to be addressed further in the future. For example, one study found that increased social deprivation led to increased barriers to accessing treatment for nAMD and hospital eye services (Sharma *et al.,* 2014).

5.3 Variation nationally in patients being treated with anti-VEGF therapy for nAMD in the UK

The second aim of this thesis was addressed by finding that there was a significant amount of variation in visual outcomes nationally in the UK in patients with nAMD. This was reflective of both clinical trial and real-world data in other studies in this field. This finding also sits within a much wider picture of unexplained variation in other health conditions nationally.

Real-world data is a very useful tool in research, as it provides a more realistic picture than perhaps clinical trial data do. This is because there are less stringent controls in terms of treatment patterns and inclusion criteria than in studies of real-world patients. However, real-world data often makes meaningful research more difficult because it has to compete with the challenges of a busy clinic or hospital department, where collection of extensive demographic and clinical data is not always a priority, due to

clinical pressures. However, this thesis has highlighted the need for further standardisation in the way that real-world data is collected. Although there is a strong argument for the difficulties of accurately recording potential research data while working in a busy clinical environment, there is an equally strong argument for collecting accurate real-world data in order to understand and improve health outcomes in the long-term. This has begun to be addressed by the Royal College of ophthalmologists in their National Ophthalmology Database standards, which seeks to establish a minimum dataset to be collected in routine clinical care (Royal College of Ophthalmologists, 2022). These guidelines stipulate mandatory, desirable and optional information. The mandatory data to be collected includes unique anonymous patient identifier, age, sex, provider organisation, site at which treatment took place, date of receipt of initial referral, assessment date, date of start of treatment, baseline distance visual acuity, date of baseline visual acuity, eye laterality, choroidal neovascularisation, intra-vitreal treatment, type of professional administering treatment, planned follow-up interval, distance visual acuity at 12 and 24 months and ocular complications of anti-VEGF therapy (Royal College of Ophthalmologists, 2022).

The data generated by this thesis followed the well-established pattern of visual progression in patients being treated with anti-VEGF therapy for nAMD, namely an initial steep rise in visual acuity at the start of treatment, followed by a more gradual decrease in the long-term. However, smaller studies or datasets that this thesis dwelt upon, resulted in a much more erratic pattern of visual progression, with much lower visual outcomes at the end of the study period. It is acknowledged in this thesis that where conversions in visual acuity measurements had to be made, that this does have its inherent problems, and it is possible that this has occurred in this thesis. The general trend of higher social deprivation levels leading to poorer visual outcomes does seem an area of importance that needs to be explored further in the future.

5.4 The relationship between visual outcomes and patient-reported quality of life outcomes

The third aim of this thesis was unable to be determined, as a significant relationship between visual outcome and self-reported quality of life outcomes was not established. However, this does not mean that such a relationship does not exist, but due to a vastly reduced sample size, it was impossible to do this in this thesis. However, it did show some general trends, such as older age at start of treatment showing a general trend towards lower quality of life outcomes being reported, which

fits with the general trend of increasing age being associated with lower quality of life outcomes. This thesis also recognises that short-term, prospective data on visual acuity often does not follow a linear pattern, in that visual acuity will often fluctuate at each visual assessment, and this is likely to have been reflected in this thesis.

5.5 Reflection on current clinical services

It is acknowledged from first-hand experience how ophthalmology services in the NHS strive to provide the best and most appropriate level of treatment for patients with nAMD. However, due to an ageing population, and therefore a greater need to treat more patients for nAMD, the findings of this thesis, across all chapters, reflects the wider literature that suggests that services struggle to cope with demand. Unfortunately, this is a problem that is unlikely to ease in the short-term, unless alternative approaches are discovered and approved. This thesis identified that adhering to the optimal number of injections per year effectively reduces significant visual loss in nAMD. However, the findings from this thesis have demonstrated how in clinical practice, rather than clinical trials, this is often not achieved. This is an issue that needs to further addressed in the future, as services at present will have to be able to cope with increasing demands for treatment provision in patients with nAMD.

This thesis established that both in retrospective real-world data and in a prospective cohort study, there were unexplainable variations in visual outcomes in patients with nAMD being treated with anti-VEGF therapy. This is important because it suggests that there may be factors or service issues that affect success of treatment that are currently being missed or that have been impossible to investigate meaningfully. If this is the case, then treatment for nAMD may have had many missed opportunities to save the sight of patients. If there are addressable factors that can optimise treatment success across all patients with nAMD, then future research needs to further explore this. However, the variation in visual outcomes in nAMD identified in this thesis sit within a much wider picture of variation in health outcomes across a

wide range of conditions, as highlighted by the Lord Carter Report (Carter, 2015). Findings of unexplained variation in visual outcomes in patients with nAMD need to be added to the wider literature on unwarranted variations in healthcare outcomes generally.

5.6 Future treatments for nAMD

During the completion of this thesis, there were developments in future treatments to the treatment of nAMD. One of the most recent of these is the potential for gene therapy (Mellen *et al.,* 2021). Brolicizumab launched with poor uptake due to ocular side effects. There is also the possible introduction of Faricimab. This treatment is being proposed as an alternative to traditionally used anti-VEGF agents, as it provides the potential to reduce the need for treatments to be repeated to at least 12 weeks in suitable patients (Sharma *et al.,* 2019). Both of these potential future treatments have the potential to change the treatment burden of nAMD in NHS settings. It was felt important that during the writing of this thesis that new and upcoming potential treatments for nAMD were kept abreast of. Particularly as such treatments could drastically change demand on clinical services for nAMD. The increased use of artificial technology may also play a part in future treatment regimens, although this is yet to be further explored. But developments such as those mentioned need to be considered in looking forward at how to take research in this field forward.

5.7 Future research steps

The next logical step of this thesis is to continue to investigate further how factors that affect anti-VEGF effect in treating nAMD can be identified and addressed, perhaps using larger sample sizes. It would also be prudent to address the inconsistency of statistical reporting in nAMD research. A larger number of sites that are willing to give retrospective data could also be helpful, in order to have more data of which to analyse. Also, a much larger prospective cohort needs to be undertaken, in order to be able to derive more statistically meaningful results. As part of any future prospective study, more sites would be recruited, and questionnaires by telephone would be utilised as discussed earlier in this chapter. In addition, it is recognised that although individual factors were explored, in future it would be prudent to explore these issues further in a closer relationship to each other, as perhaps intersectionality may be playing a part in visual outcomes. However, any future research would have

to take into consideration the latest developments in nAMD treatments; any future research will be facilitated and funded by a postdoctoral lectureship that has already been secured, to be commenced after the submission of this thesis.

5.8 Final conclusions

The importance of clinical trials in determining visual acuity in treatment for nAMD with anti-VEGF therapy has been well established. However, the research presented in this thesis further adds to the evidence from current literature that clinical services in the NHS fail to replicate the visual outcomes achieved in clinical trials. This thesis has highlighted the importance of early diagnosis, in terms of age and visual acuity at baseline, and number of injections received as important factors for better visual outcomes for patients with nAMD. This thesis also identified variations in outcome of visual outcomes of patients being treated for nAMD, despite the problems of working with a large real-world dataset. However, it was not established that social deprivation had any meaningful effect on visual outcomes nor was any relationship identified between visual outcomes and self-reported quality of life. However, in future research, this result may be remedied by using a larger prospective cohort of patients, and strengthened research methods. But overall, this thesis has highlighted that there are still a lot of unknowns about how to optimize treatment for nAMD, and how this is related to quality of life for patients.

Appendices

1. EXAMPLE OF A SEARCH STRATEGY

Ovid MEDLINE will be searched with the following search terms. The search will begin in the year 2005 because this is the year in which anti-VEGF agents were first used in clinical trials as a treatment for nAMD.

The literature search took place between January 2018 and March 2018.

Ovid CINAHL 2005 to week 1 January 2018

SEARCHES

RESULTS

1) (ranibizumab OR bevacizumab OR aflibercept)	4472
2) (lucentis OR avastin OR eylea)	385
3) exp anti vascular endothelial growth factor	2660
4) "anti-VEGF" OR "anti VEGF" "anti-vascular endothelial growth factor" OR "anti vascular endothelial growth factor"	1198
5) 1 OR 2 OR 3 OR 4	7367
6) "neovascular age related macular degeneration"	348
7) nAMD OR AMD OR "wet AMD" OR "late AMD"	1521

8) 6 OR 7 1718

9) 5 AND 8 472

10) visual response 920

11) visual N5 (effectiveness OR outcome OR acuity OR VA OR "best corrected visual acuity" OR BCVA) 17783

12) ("central retinal thickness" OR "intraretinal fluid" OR IRF OR "subretinal fluid" OR SRF)

4243

13) 10 OR 11 OR 12 221627

14) 9 AND 13 225

2. NEWCASTLE OTTAWA SCALE

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and

Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ⁻

b) somewhat representative of the average _____ in the community ⁻

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ⁻

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) ¯

b) structured interview ¯

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ¯

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) ¯

b) study controls for any additional factor ¯ (This criteria could be modified to indicate specific

control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment ¯

b) record linkage ¯

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) ¯

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ¯

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ¯

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

3. INCLUDED STUDY OUTCOMES

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
Abedi *et al*., (2013)	Mean VA change at 12 months	None	17 Single Nucleotide Polymorphisms (SNP's) from known AMD-associated risk genes	SNP rs11200638-HTRA1: mean VA change -2.9 (SE 3.8, *p*= 0.001*) SNP rs10490924 (A69S): mean VA change -2.6 (SE 3.8, *p*= 0.002*)
Airody *et al.,* (2015)	Mean VA (ETRDRS	VA and CRT	Number of visits and	Baseline = 47.0

	letters) at 60 months		number of injections	(SD=15.0). At 60 months= 52.7 (SD= 16.9, p= >0.05)
	Mean CRT (microns) at 60 months			Baseline= 328.4 (SD= 80.2). At 60 months 230.2 (SD= 48.5, p- 0.003)
	Median number of injections at 12 months and 60 months			12 months= 6. 60 months= 7

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
		-		
	Median number of visits at 12 months and 60 months			12 months= 9 60 months= 10
Bloch *et al*., (2013)	OR for male *vs.* female of BCVA in patients with baseline BCVA ≤ 35, or ≤20, or ≤70, for having BCVA ≤35 at 12 months.	BCVA at baseline and 3 months of ≤ 35 ETDRS letters, ≤20 and ≥ 7	None.	OR for male *vs.* female in patients with baseline BCVA ≤ 35= 0.6 (CI 0.31, 1.38, p= 0.264).

		Sex Age Total lesion size (for BCVA at 12 months of ≥ 70 only).		For patients with baseline BCVA ≤20= 0.4 (CI 0.15, 1.25, p= 0.123). For patients with baseline BCVA ≥ 70= 1.6 (CI 0.70, 3.57, p= 0.266).
	OR for age ≥80 *vs.* <80 for patients with baseline BCVA ≤ 35, at baseline for			OR for age ≥80 *vs.* <80 for patients with BCVA ≤ 35 at baseline for 12- month

	12- month BCVA ≤ 35, <20			

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	and ≥ 70, for having BCVA ≤35 at 12 months.			BCVA ≤ 35= 0.8 (CI 0.39, 1.60, p= 0.519. For patients with baseline BCVA ≤20= 0.7 (CI 0.28, 1.81, p= 0.473).

				For patients with baseline BCVA ≥ 70= 0.9 (CI 0.39, 1.94, p= 0.725).
	OR of BCVA at baseline ≤ 35, ≤20 and ≥ 70, predicting BCVA at 12 months ≤ 35.			OR of BCVA at baseline ≤ 35 predicting BCVA at 12 months ≤ 35= 10.6 (CI 4.11, 27.16. P= <0.0001). BCVA of≤ 35 at 3 months for predicting BCVA of ≤ 35 at 12 months OR= 16.3 (CI 5.01, 53.13, P=

				<0.0001. OR Baseline and month 3 BCVA ≤ 35 for predicting BCVA≤ 35 at 12

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome

				months = 91.6 (CI 20.28, 413.66, p= <0.001). OR of BCVA ≤20 predicting BCVA at 12 months ≤20= 4.3 (CI 1.03, 17.74, p= 0.045) At 3 months OR = 12.5 (CI 3.04, 51.78, p-<0.0001). Baseline and month 3= 10.80, 90.20, p= <0.0001).

				OR of BCVA ≥ 70 predicting BCVA at 12 months ≥ 70= 23.7 (CI 4.22, 133.29, p= 0.0003) At 3 months OR= 17.7 (CI 7.41, 42.43, p= <0.0001). Baseline and month 3= 107.1 (CI 26.28, 436.56, p= <0.0001).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	OR of total lesion size predicting BCVA ≥70 at 12 months.			OR= 3.0 (CI 1.25, 7.40, p= 0.0147).

Brown *et al* (2013)	Mean change in BCVA at month 24 in eyes with baseline lesion sizes <4 DA and ≥4 DA.	Baseline fundus fluorescein angiography lesion size and composition. (Total lesion area categorised as ≤ 4 and >4 DA. CNV lesion composition classified as predominantly classic, minimally classic, and occult without classic).	Quantitative optical coherence tomography (eyes with CFT <200 um and CFT ≥ 200 um. Qualitative OCT (eyes with active OCT lesions, or inactive OCT lesions).	Lesion size <4 had a mean change of -0.10 compared with -4.3 in lesion size ≥4 (p= 0.13).
	Loss of ≤15 letters of BVCVA from baseline to			16% of eyes with lesion size ≤4 lost ≤15 ETDRS

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	month 24 in eyes with lesion ≤4 DA and >4.			letters compared with 23% in eyes with lesion size >4.
	Mean change in BCVA letters from baseline to month 24 in eyes with minimally classic CNV, occult with no classic CNV, and predominantly classic CNV.			Mean change of -3.1 in eyes with minimally classic CNV, -2.0 in eyes with occult with no classic CNV, and -1.4 in eyes with predominantly classic CNV (p= 0.90).

	Gain of ≥15 letters from baseline to month 24 in eyes with minimally classic CNV, occult with no classic CNV, and predominantly classic CNV.			24% of eyes with predominantly classic CNV gained 15≥ letters at month 24, compared with 10% of eyes with the other compositions of lesions (p= 0.44).
	4-letter difference from baseline to month 24 in eyes with active and inactive FFA lesions.			Not significant (p= 0.36).
	Letters gained from baseline to month 24 in			Eyes with inactive lesions gained 11.3 more letters at

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	eyes with active and inactive FFA lesions.			month 12 than those with active lesions, and 7.9 more letters at month 24 (p=0.093).

	Average gain in letters from baseline in eyes with CFT <200um compared to those with ≥200 um.			Eyes with CFT <200 um at month 3 gained an average of 2.87 more letters at 12 months (p= 0.45) and 3.58 more letters at month 24 (p= 0.41) compared to those with CFT ≥200 um. In eyes with CFT <200 um at month 5, there was an average gain of 4.22 letters at month 12 (p=0.20), compared with eyes with a CFT ≥200 um.
	Mean change in BCVA from baseline to 12 and 24 months in eyes with active			No significant difference between eyes with active and inactive lesions at month 12 (p= 0.91) and month 24 (p= 0.84). At

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	FFA lesions and inactive FFA lesions.			month 12, the BCVA difference between the active and non-active FFA lesions groups was significant (p= 0.0045).

	Letters gained from baseline in eyes with active FFA lesions and inactive FFA lesions.			Eyes with inactive lesions at month 3 gained an average of 5.65 more letters at month 12 (p= 0.091) and 4.41 more letters at month 24 (p= 0.22) compared to active lesions at month 24. Eyes that had inactive lesions at month 5 gained an average of 3.29 more letters at month 12 (p= 0.33) compared to those who had active lesions. Eyes that had inactive lesions at month 8 gained an average of 5.88 more letters at month 12 (p=

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				0.09) compared to those with active lesions. Eyes that had inactive lesions at month 8 gained an average of 9.54 more letters at month 24 (p= 0.009) compared to those with active lesions at month 8.

Calvo *et al.,* (2015)	Proportion of patients at 36 months who did not have a worsening of BCVA from baseline of more than 0.3 logMAR units at 36 months in eyes that had ≥7 or <7 injections.	None.	Number of injections (≥ 7 or 7).	For eyes receiving ≥7 injections proportion was 88.9%, compared to 60.7% for eyes receiving <7 injections.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Proportion of patients at 36 months who had BCVA from baseline that remained stabled or got better in eyes that had ≥7 or <7 injections.			At 36 months, the proportion of patients who had a BCVA that remained stable or became better was 92.9% for those having ≥ 7 injections compared to 51.4% of those having < 7 injections.

Chae *et al.,* (2015)	Age at first injection as a predictor of good vs poor response.	Age at first injection, Anatomic classification, aspirin use, bilaterality, choroidal atrophy, CNV localisation, Warfarin, diabetes, family history of AMD, Fluorescein angiography classification, glaucoma, greatest linear diameter, hypertension, overall lesion area, clopidogrel, sex, smoking history, statins, visual acuity at presentation.	Injection mean interval, no. of injections at 3, 6, 12, 24, 36, and 48 months, visual acuity at 3, 6, 12, 24, 36 and 48 months.	Age at first injection as a predictor for response at 2 years p= 0.126**. Age of first injection as a predictor for response at 3 years p= 0.262. Age of first injection as a predictor for response at 4 years p= 0.090.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Aspirin use as a predictor of good vs poor response.			Aspirin use as a predictor for response at 2 years p= 0.545. Aspirin use as a predictor for response at 3 years p= 0.141. Aspirin use as a predictor for response at 4 years p= 0.215.

	Bilaterality as a predictor of good vs poor response.			Bilaterality as a predictor for response at 2 years p= 0.790. Bilaterality as a predictor for response at 3 years= 0.643. Bilaterality as a predictor for response at 4 years= 0.586.
	Choroidal atrophy as a predictor of good vs poor response			Choroidal atrophy as a predictor for response at 2 years p= 0.461.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				At 3 years p= 0.145. At 4 years p= 0.364.
	CNV localisation as a predictor of good vs poor response.			CNV localisation as a predictor for response at 2 years p= 0.377. At 3 years p= 0.936. At 4 years p= 1.00.

	Warfarin use as a predictor of good vs poor response.			Warfarin use as a predictor for response at 2 years p= 0.233. At 3 years p= 0.349. At 4 years p= 0.630.
	Diabetes as a predictor of good vs poor response.			Diabetes as a predictor for response at 2 years p= 0.410. 3 years= 0.728. 4 years= 0.216.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Family history of AMD as a predictor for good vs poor response.			Family history of AMD as a predictor for response at 2 years p= 0.433. At 3 years p= 0.790. At 4 years p= 0.801.
	Glaucoma as a predictor for good vs poor response.			Glaucoma as a predictor for response at 2 years p= 0.534. At 3 years p= 0.263. At 4 years p= 1.000.

	Greatest linear diameter as a predictor for good vs poor response.			Greatest linear diameter as a predictor for response at 2 years p= 0.376. At 3 years p= 0.623. At 4 years p= 0.285.
	Hypertension as a predictor for good vs poor response.			Hypertension as a predictor for response at 2 years p= 0.036. At 3 years p= 0.138.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				At 4 years p= 0.223.
	No. of injections at 3 months as a predictor for good vs poor response.			No. of injections at 3 months as a predictor for response at 2 years p= 0.265. At 3 years p= 0.777. At 4 years p= 0.841.

	No. of injections at 6 months as a predictor for good vs poor response.			No. of injections at 6 months as a predictor for response at 2 years p= 0.194. At 3 years p= 0.291. At 4 years p= 0.114.
	No. of injections at 12 months as a predictor for good vs poor response.			No. of injections at 12 months as a predictor for response at 2 years p= 0.021. At 3 years p= 0.291. At 4 years p= 0.197.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	No. of injections at 24 months as a predictor for good vs poor response.			No. of injections at 24 months as a predictor for response at 2 years p= 0.006. At 3 years p= 0.083. At 4 years p= 0.102.
	No. of injections at 36 months as a predictor for good vs poor response.			No. of injections at 36 months as a predictor for response at 3 years p= 0.017. At 4 years p= 0.052.

	No. of injections at 48 months as a predictor for good vs poor response.			No. of injections at 48 months as a predictor for response at 4 years p= 0012.
	Overall lesion area as a predictor for good vs poor response.			Overall lesion area as a predictor for response at 2 years p= 0.107. At 3 years p= 0.671. At 4 years p= 0.446.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Clopidogrel use as a predictor for good vs poor response.			Clopidogrel use as a predictor for response at 2 years p= 0.04. At 3 years p= 0.318. At 4 years p= 0.024.
	Sex as a predictor for good vs poor response.			Sex as a predictor for response at 2 years p= 0.568. At 3 years p= 0.270. At 4 years p= 0.487.

	Smoking history as a predictor of good vs poor response.			Smoking history as a predictor for response at 2 years p= 0.115. At 3 years p= 0.441. At 4 years p= 0.442.
	Statins use as a predictor of good vs poor response.			Statins use as a predictor for response at 2 years p= 0.840. At 3 years p= 0.532.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				At 4 years p= 0.399.
	Injection mean interval as a predictor of good vs poor response.			Injection mean interval as a predictor for response at 2 years p= 0.000. At 3 years p= 0.010. At 4 years p= 0.004.
	Injections per year as a predictor of good vs poor response.			Injections per year as a predictor for response at 2 years p= 0.000. At 3 years p= 0.003.

				At 4 years p= 0.006.
	Visual acuity at baseline as a predictor of good vs poor response.			Visual acuity at baseline as a predictor for response at 2 years p= 0.000. At 3 years p= 0.000. At 4 years p= 0.000.
	Visual acuity at 3 months as a predictor of good vs poor response.			Visual acuity at 3 months as a predictor for response at 2 years p= 0.000.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				At 3 years p= 0.000. At 4 years p= 0.000.
	Visual acuity at 6 months as a predictor of good vs poor response.			Visual acuity at 6 months as a predictor for response at 2 years p= 0.000. At 3 years p= 0.000. At 4 years p= 0.000.

	Visual acuity at 12 months as a predictor of good vs poor response.			Visual acuity at 12 months as a predictor for response at 2 years p= 0.000. At 3 years p= 0.000. At 4 years p= 0.000.
	Visual acuity at 2 years as a predictor of good vs poor response.			Visual acuity at 2 years as a predictor for response at 3 years p= 0.000. At 4 years p= 0.000.
	Visual acuity at 3 years as a predictor of good vs poor response.			Visual acuity at 3 years as a predictor for response at 4 years p= 0.000.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
Chatziralli *et al*., (2016)	Co-efficient of male vs female gender as a predictor of good vs poor response.	Age (10-year increase), gender (male vs female), CRT (100-um increase), SRF only (SRF ns no fluid), IRF only (IRF vs no fluid), both SRF and IRF (both vs no fluid), ORT, PED, HF, atrophy, subfoveal thickening, vitreomacular traction, ERM	No. of previous ranibizumab injections (1 injection increase), bilateral administration.	-1.73 (-4.67, 1.20) p= 0.248.
	Co-efficient of no. of previous bevacizumab injections as a predictor of good vs poor response.			0.26 (-0.04, 1.20) p= 0.088.

	Co-efficient of SRF as a predictor of good vs poor response.			0.07 (-1.05, 1.19) p= 0.900.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Co-efficient of ORT as a predictor of good vs poor response.			0.91 (-0.91, 2.73) p= 0.325.
	Co-efficient of HF as a predictor of good vs poor response.			-0.88 (-2.01, 0.24) p= 0.122.
	Co-efficient of atrophy as a predictor of good vs poor response.			-0.57 (-1.93, 0.80) p= 0.417.

	Co-efficient of vitreomacular traction as a predictor of good vs poor response.			0.75 (-1.65, 3.15) p= 0.538.
	Co-efficient of ERM as a predictor of good vs poor response.			-1.32 (-3.04, 0.40) p= 0.133.
	Co-efficient of bilateral administration as a predictor of good vs poor response.			-3.11 (-8.71, 2.49) p= 0.276

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Co-efficient of age as a predictor for good vs poor response.			-3.72 (-5.46, -1.98) p=<0.001.
	Co-efficient of CRT as a predictor for good vs poor response.			-0.77 (-1.41, -0.13) p=0.018.
	Co-efficient of IRF as a predictor of good vs poor response.			-0.96 (-1.90, -0.01) p=0.049.

	Co-efficient of both SRF and CRT as a predictor for good vs poor response.			2.14 (-3.34, -0.94) p=<0.001.
	Co-efficient of PED as a predictor of good vs poor response.			-1.37 (-2.58, -0.16) p=0.027.
	Co-efficient of subfoveal thickening as a predictor for good vs poor response.			-2.32 (-3.77, -0.87) p=0.002.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
Chabblani *et al*., (2015)	Pre-treatment BCVA as a predictor of visual outcome at 6 months.	Pre-treatment BCVA, pre-treatment CMT, CNV type, lesion size, pre-treatment IS/OS junction damage, pre-treatment ELM damage.	None.	P= 0.21.
	Pre-treatment CMT as a predictor of visual outcome at 6 months.			P= 0.81
	CNV type as a predictor of visual outcome at 6 months.			P= 0.49.

	Lesion type as a predictor of visual outcome at 6 months.			P= 0.23
	Pre-treatment IS/OS junction damage as a predictor of visual outcome at 6 months.			P= 0.085
	Pre-treatment ELM damage as a predictor of			p= 0.0145

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	visual outcome at 6 months.			
Chaprek *et al*., (2015)	Gender proportions in the active lesion group and inactive lesion group.	Gender, age, type and size of CNV lesion, baseline BCVA and baseline macular thickness.	None.	active group 37.9% male, 62.1% women. Inactive group 41% men and 59% women (p= 0.338).

	Proportions of those aged <70 years, 70-80 years, and >70 years in the active lesion group and inactive lesion group.			Active group 29.3% and inactive group 27.9% age <70 years. 43.4% and 42.9% aged 70-80 years. 27.3% and 29.2% aged >70 years (p= 0.237).
	Difference between median baseline BCVA in the active lesion group and inactive lesion group.			The median of the baseline BCVA was 54 (5– 95 percentiles: 22– 73) and 55 (5–95 percentiles: 23–75) in the active and inactive

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				group, respectively. P= 0.066.
	Difference between the median CMT in the active lesion group and inactive lesion group.			The median of the baseline macular thickness was 330.um (5– 95 percentiles: 190–600) and 337um (5–95 percentiles: 201–535) in the active and inactive group, respectively. P= 0.663.

	Difference in lesion type between the active lesion group and inactive lesion group.			The active and the inactive group included 31% and 20.2% of patients with predominantly classic CNV, 21% and 19.9% with minimally classic CNV, and 47.9% and

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				59.9% with occult CNV, respectively. The inactive group showed statistically significantly higher presence of occult membranes and statistically significant lower presence of predominantly classic CNVs compared with the

				active group (p= 0.001).
	Difference in lesion size between the active lesion group and inactive lesion group.			Lesion size: The active and the inactive group included 23.8% and 26.9% of patients with CNV < 2 disc areas (DA), 66.8%

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				and 70.2% of patients with CNV 2–5DA, 9.4% and 2.9% of patients with CNV > 5DA, respectively. The inactive group showed statistically significantly lower presence of CNV > 5DA compared with the

				active group ($PP <$ 0.001).
El Mollayess *et al.,* (2013)	Difference in decrease in CRT between each group (group 1 >70 letters at baseline, group 2 70-61 letters, and group 3 60 to 51 letters).	Baseline VA	None	P= 0.964.
	Difference in BCVA letters gained at 12 months in each group (group 1 >70 letters at baseline, group 2			BCVA: group 1 +0.4 letters, group 2 +3.8

				letters, group 3 +4.2 letters (p= 0.42).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	70-61 letters, and group 3 60 to 51 letters).			
	Difference in proportion of eyes gaining 15 or more letters at 12 months in each group (group 1 >70 letters at baseline, group 2 70-61 letters, and group 3 60 to 51 letters).			4/30 eyes in G2, 13/30 eyes in G3 and 0 eyes in G1 gained 15 or more letters in BCVA. Significant difference between groups G3 and Gp 1 and only (p= <0.001 and p= 0.01 respectively).

	Difference in proportion of eyes that avoided losing 15 letters at 12 months in each group (group 1 >70 letters at baseline, group 2 70-61 letters, and group 3 60 to 51 letters).			In Gp 1 all 30 eyes avoided losing 15 letters in BCVA, and in Gp 3 24/30 eyes avoided losing 15 letters of BCVA (p= 0.02).
	Difference in mean CRT decrease in each group at 12 months (group 1 >70 letters at baseline, group 2			Gp 1 -99.5 um, Gp 2 -96.0, Gp 3 -94.9 (p= <0.001 for each group).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	70-61 letters, and group 3 60 to 51 letters).			

Essex *et al*., (2016)	Length of treatment interval at first reactivation of lesion.	None.	Treatment interval at first reactivation, time to first reactivation, VA change.	Eyes with a short induction phase were subsequently active at 26% of visits during the maintenance phase, compared with 33% in longer induction- phase eyes, though this difference was not significant (P 0.105).
	Time to reactivation of lesions between longer and shorter induction phase groups.			Longer-induction-phase eyes

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				reactivated sooner than short-induction-phase eyes, with a mean of 239 days (median 202 days) compared with 405 days (median 367 days) (P= 0.001)
Fang *et al*., (2013)	Duration of nAMD as a predictor of ≥15 letters from baseline BCVA to 6 months.	Age, baseline VA score, gender, smoking, lesion type.	None.	p= 0.092

	OR for gaining ≥15 letters from baseline BCVA to 6 months between patients with a baseline of 40-59 letters, and those with a baseline of >60 letters.			Compared with pts whose baseline VA was < 20 letters, the OR for gaining 15 or more letters for pts with baseline VA 0f 40-59 letters was 0.277 (0.081, 0.944) and it was 0.107 (0.018, 0.638 in pts with a baseline of > 60 letters.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Age as a predictor of ≥15-letter Gain from Baseline at 6 Months.			p= 0.028
	Baseline VA as a predictor of≥15-letter Gain from Baseline at 6 Months.			p= 0.001
	Duration of nAMD as a predictor of≥15-letter Gain from Baseline at 6 Months.			p= 0.02

	Rs10490924 genotype as a predictor of≥15-letter Gain from Baseline at 6 Months.			P= 0.021
	Smoking history as a predictor of CRT change from baseline to 6 months.			Never smokers (-106.5 um) compared with -56.0 um in ex or current smokers (p= 0.047).
Gupta *et al*., (2011)	Mean VA change at 3, 6, 9, and 12 months for the LD group and PRN group.	Sex, age laterality, symptom duration, lesion type, baseline VA, OCT central thickness, OCT	Treatment regimen.	3 months – LD= 48 (SD 15.25). PRN= 44.48 (SD 15.41). 6 months – LD= 55.46 (SD 18.68). PRN=

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
		central volume, SRF, IRF, PED, lesion size, and lens status.		49.64 (SD 18.69). 9 months – LD= 51.29 (SD 19.61). PRN= 49.74 (SD 19.72). 12 months – LD= 52.44 (SD 20.29). PRN= 48.51 (SD 20.38).
	Co-efficient and SE of sex as a predictor of 12-month visual outcome.			6.825, 3.578, 0.0609, (-0.321, 13.970).

	Co-efficient and SE of age as a predictor of 12-month visual outcome.			-0.106, 0.238, 0.6576, -0.580, 0.369).
	Co-efficient and SE of laterality as a predictor of 12-month visual outcome.			-0.656, 3.711, 0.8602, (-8.067, 6.755).
	Co-efficient and SE of symptom duration as a predictor of 12-month visual outcomes.			-1.335, 0.900, 0.1429, (-3.134, 0.463).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Co-efficient and SE of lesion type as a predictor of 12-month visual outcome.			-1.136, 1.676, 0.5006, (-4.484, 2.212).
	Co-efficient and SE of baseline BCVA as a predictor of 12-month visual outcomes.			0.953, 0.135, 0.2000, (0.683, 1.223).
	Co-efficient and SE of OCT central thickness as a predictor of 12-month visual outcomes.			0.0461, 0.0348, 0.1903, (-0.0235, 0.1156).

	Co-efficient and SE of OCT central volume as a predictor of 12-month visual outcomes.			1.756, 1.992, 0.3814, (-2.223, 5.734).
	Co-efficient and SE of SRF as a predictor of 12-month visual outcomes.			13.692, 6.887, 0.0510, (-27.446, 0.063).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Co-efficient and SE of IRF as a predictor of 12-month visual outcomes.			0.757, 3.785, 0.8422, (-6.803, 8.317).
	Co-efficient and SE of PED as a predictor of 12-month visual outcomes.			3.367, 3.626, 0.3565, (-3.874, 10.609).
	Co-efficient and SE of lens status as a predictor of 12- month visual outcomes.			0.515, 5.740, 0.9288, (-10.948, 11.978).

Gale *et al*., (2016)	Proportion of patients with the presence of blood in the early and late- responders' groups.	Mean VA baseline, presence of PED, presence of blood.	None.	Early= 90.2/266, late= 84.1/135 p=0.08 for both (HARBOR).
	Proportion of patients with lower mean baseline VA in the early and late responders.			Early= 43/82, 47/53 p= <0.05 (ANCHOR and MARINA). 50/266 p= <0.001 (HARBOR). Late= 55/135 p= <0.001 (HARBOR).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Proportion of late responders with presence of PED.			58.5/135 p= 0.007 (HARBOR).

Guber *et al*., (2014)	Mean change in baseline BCVA in patients aged 50- 75 years compared with those aged ≥75.	Gender (women-men) Age (≥ 75 - <74) Initial BCVA (logMAR) (≥0.4 - <0.3). Lesion type (occult – classic) Maculae oedema type (IRF□RCRT, spongoid type IRF□RCRT, cystoid type IRF□RCRT, SRF□ RCRT, PED□RCRT).	None.	4.93, (±8.79), p= 0.27.
	Mean change in BCVA from baseline in patients with baseline BCVA of ≥4.0, compared to those			-3.34, (±7.18), p= 0.36.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	with a baseline BCVA of 3.0 – 0.0.			
	Mean change in BCVA from baseline in patients with classic versus occult lesions.			1.24, (±6.7), p= 0.70

	% Change from RCRT according to macular oedema type (SRF, IRF, PED, spongid type IRF, cystoid type IRF).			SRF: 28.97, (±9.34). PED: 27.61, (±10.61). IRF: 35.72, (±10.8), p= <0.001. Spongoid type IRF: 44.26, (±10.76), p= 0.001. Cystoid type IRF: 27.17, (±10.86), p= 0.001
	Mean change in BCVA in male vs female patients.			-6.47, (±6.56), p= 0.05.
Holz *et al*., (2016)	Co-efficient and SE for age as a predictor for change in VA at year 1 and year 2.	Age at start of therapy. VA at baseline.	No. of injections.	Y1: -0.106, 0.081, (-0.265, 0.052), p= 0.188.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				Y2: -0.177, 0.081, (-0.335, -0.018), p= 0.029.
	Co-efficient and SE for no. of injections as a predictor for change in VA at year 1 and year 2.			Y1: 5.409, 1.514, (2.441, 8.377), p= <0.001. Y2: 1.933, 0.552, (0.852, 3.015), p= <0.001.

	Co-efficient and SE for VA at baseline as a predictor for change in VA at year 1 and year 2.			Y1: -0.279, 14.380, (-0.352, -0.206), p= <0.001. Y2: -0.391, 0.035, (-0.459, -0.322), p= <0.001.
Jonas *et al*., (2011)	Elevated RPE height in group 1 vs group 2 at 3 months.	Baseline BCVA (group 1: higher VA. Group 2: lower VA).	None.	G1: 126 (±120). G2: 155 (±150). P= 0.24.
	Subretinal fluid height in group 1 vs group 2 at 3 months.			G1: 39 (±67). G2: 40 (±80). P= 0.96.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Highest retinal thickness of macula in group 1 vs group 2 at 3 months.			G1: 329 (±139). G2: 326 (±80). P= 0.82.
	Difference in BCVA at 3 months in group 1 vs group 2.			G1: 0.49 (±0.38). G2: 0.80 (±0.45). P= <0.001
	Change in BCVA at 3 months in group 1 vs group 2.			G1: 0.05 (±0.29). G2: -0.07 (±0.25). P= 0.02.

Korb *et al.,* (2013)	OR of being a reduced responder at 3 months in patients with presence of PED at baseline.	Initial CNV size, initial PED, initial CRT, initial type of lesion (1. minimally classic vs occult, 2. predominantly classic vs occult, 3. RAP vs occult), age, time between first consultation to treatment (days).	None.	1.728, (0.595, 5.024), p= 0.315.
	OR of baseline CRT influencing patients being			0.998, (0.994, 1.002), p= 0.362.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	a reduced responder at 3 months.			
	OR of type of lesion (minimally classic vs occult, predominantly classic vs occult, RAP vs occult) influencing patients being a reduced responder at 3 months.			Minimally classic vs occult: 0.886, (0.312, 2.518), p= 0.820. Predominantly classic vs occult: 0.966, (0.437, 2.135), p= 0.932. RAP vs occult:1.597, (0.570, 4.471), p= 0.373.

	OR of age of patient in years influencing patients being a reduced responder at 3 months.			0.986, (0.943, 1.030), p= 0.528.
	OR of time to first injection influencing patients being a reduced responder at 3 months.			0.995, (0.981, 1.009), p= 0.452.
	OR of baseline CNV size influencing patients being			0.964, (0.936, 0.993), p= 0.017.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	a reduced responder at 3 months.			
Ozkaya *et al*., (2014)	Difference between baseline BCVA and 3, 6, 9, and 12 months BCVA.	PED at baseline. Baseline VA. Lesion type. Baseline IOP.	No. of injections.	BCVA 3,6, 9, 12 months: 0.19±0.10. p= <0.0001. 0.23±0.16 (P=0.44), 0.25±0.18 (P= 0.74), 0.23±0.15 (P= 0.67).

	Correlation between BCVA change and lesion type at 3, 6, 9 and 12 months.			P= 0.15 for all time points.
	Correlation between BCVA change at 6, 9 and 12 months and IOP.			Month 12: 15.9±1.9. P= 0.07.
	Difference from baseline in CRT at 3, 6, 9, and 12 months.			P= <0.001 for all time points.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Correlation between BCVA change and no. of injections at 12 months.			Month 12: P= 0.001.
	Correlation between change in BCVA and presence of PED at baseline.			P= <0.01 for all time points.
Razi *et al*., (2016)	Correlation between baseline VA and change in VA from baseline to 36 months.	Baseline VA.	No. of injections.	p=<0.001.

	Correlation between no. of injections and change in VA from baseline to 36 months.			P= 0.036.
Regillo *et al.,* (2015)	Difference in letters gained from baseline at 12 months between patients with baseline BCVA of ≤44 letters vs those with BCVA of >44 letters.	Baseline BCVA. Age. CNV leakage area. SRF presence.	None.	Baseline BCVA ≤44 letters gained 15.3 letters compared with 8.2 in patients with baseline BCVA >44.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Difference in letters gained from baseline at 12 months between patients aged ≤73 years vs those aged >73.			Patients aged ≤73 gained a mean 13.1 letters compared with a mean of 8.6 letters in pts >73.
	Difference in letters gained from baseline at 12 months between patients with CNV lesion area of ≤5.24 DA and those with lesion area >5.47.			CNV leakage area ≤5.24 DA and ≤5.47 CNV area gained +10.7 more letters than pts with >5.47 DA area and >5.24 leakage.

	OR of patients gaining >15 letters from baseline at 12 months if SRF present at baseline.			SRF present: present at baseline, 41% of those with baseline total CNV leakage area <4.51 DA (n ¼ 282) gained >15 letters at month 12 vs 22% of patients with baseline total CNV

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				leakage area >4.51 DA (n ¼ 99; OR, 2.5; 95% CI 1.5– 4.3

Rosenfeld *et al.,* (2011)	Association of area of leakage with vision loss after 2 years.	Age, VA, total lesion area, total CNV area, CNV leakage area, % of lesion with classic CNV, total area of blood, Area of subretinal fibrosis/scar, area of GA, area of RPE abnormality, incidence of RPE tears.	None.	No increase in area of leakage in ANCHOR (p= 0.17).
	Association of baseline BCVA with vision loss after 2 years.			VA losers had better baseline VA than VA gainers (MARINA P= 0.008, ANCHOR P= 0.014).

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Association of age, lesion size and CNV leakage with vision loss after 2 years.			Age, lesion size and CNV leakage: (MARINA P= 0.011, ANCHOR P= 0.014) VA losers tended to be older and have larger lesions at baseline and larger areas of leakage (MARINA P= 0.0073, ANCHOR P= 0.0071).

	Association of RPE abnormalities with vision loss after 2 years.			VA losers had increased areas of RPE abnormalities compared with VA gainers at month 24 (MARINA P= 0.008, ANCHOR P= 0.0046).
	Association between total lesion area and vision loss after 2 years.			Total lesion area: increased more among VA

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				losers (MARINA P= 0.017, ANCHOR P= 0.0055).
	Association between area of atrophic scar and vision loss after 2 years.			Area of atrophic scar: increased in VA losers in MARINA and accounted for increase in lesion area (MARINA P= 0.043). In ANCHOR, increase in total area of CNV accounted for this (P= 0.039).

	Association between RPE tears and vision loss after 2 years.			RPE tears: in MARINA, RPE tears 9.5% in VA losers compared with 1.4% in VA gainers at months 12 and 24 (P= 0.025).
Rush *et al.,* (2014)	Difference between mean baseline BCVA and final mean BCVA at 12 months.	Age, phakic status, posterior vitreous detachment status,	None.	Mean baseline BCVA Snellen 20/55 (0.44 log MAR) (0.41-0.47). Mean final BCVA: Snellen 20/44,

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
		baseline BCVA, baseline CMT, and type of CNV.		0.35 logMAR (0.27, 0.43), P= <0.001).
	Difference between mean baseline CMT and final mean CMT at 12 months.			Mean baseline CMT 373.1 um (360.3-385.9. Mean final CMT: 305.5 um (290.0, 316.0 um), P=

				<0.001.
Shona *et al.*, (2011)	Baseline VA as a predictor for poor VA at 3, 6, 9, and 12 months.	Baseline VA.	None.	Poor VA: M3: 39.48±13.58 (P= <0.0002). M6: 43.26±12.90 (P= <0.0001). M9: 40.52±13.13 (P= <0.0002). M12: 43.67±11.72 (P= <0.0001).
	Baseline VA as a predictor of intermediate VA at 3, 6, 9 and 12 months.			Intermediate VA: M3: 48.64±11.91 (P+ 0.016). M6: 50.30±13.06 (P=

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				0.0034). M9: 49.30±14.97 (P= 0.035). M12: 50.88±15.74 (P= 0.012).
	Baseline VA as a predictor of good VA at 3, 6, 9 and 12 months.			Good VA: M3: 62.56±12.07 (P= 0.69). Good VA: M6: 66.96±10.26 (P= 0.01). M9: 65.93±9.24 (P= 0.07). M12: 64.51±9.28 (P=

				0.19).
Singh *et al.,* (2011)	Mean visual acuity change based on baseline CNV lesion type.	Baseline CRT, age, race, smoking status, underlying medical conditions.	Previous treatment.	p=0.19 at 4.5 months, p=0.28 at 6 months).
	Mean visual acuity change based on baseline CNV lesion type.			p=0.01 at 1.5 months, p=0.03 at 3 months.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	Mean central retinal thickness (CRT) change based on baseline CRT.			p=0.02 at 1.5 months, p=0.003 at 3 months, p=0.02 at 4.5 months, p=0.04 at 6 months
	Mean CRT change based on previous treatment history.			p=0.01 at 1.5 months, p=0.01 at 3 months, p=0.04 at 4.5 months, p=0.005 at 6 months

Subhi and Sorenson (2017)	Mean VA change in patients aged ≥90 years.	Age ≥90.	None.	stabilized at 12 and 24 months (mean change 1.5 (SD: 16.5) ETDRS letters, *P* = 0 342; mean change −2.2 (SD: 20.1) ETDRS letters, *P* = 0 288; one sample t-test, resp., for 12 and 24 months). anti-VEGF therapy improved the BCVA at 4

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				months (after the loading dose phase) (mean change 3.2 (SD: 15.5) ETDRS letters, *P* = 0 036; one sample t-test).

Van Asten *et al.,* (2014)	OR of non-response in male sex.	Age >80, male sex, baseline VA (1.>20/63, 2. 20/63-20/200, 3. 20/200-20/640, 4. ≥ 640), hypertension, diabetes, MI, angina, stroke or TIA, smoking ≥ 20 pack years, BMI> 30kg/m2, occult CNV with no classic, RAP, minimally classic CNV, predominantly classic CNV, lesion size <2DA, 2-4 DA, 4-6 DA, >6 DA.	None.	Male sex: 0.9 (0.5, 1.8), p= 0.862.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	OR of non-response in patients with hypertension.			1.4, (0.6, 3.3), p= 0.420.
	OR of non-response in patients with MI.			0.8, (0.1, 7.0), p= 0.860.
	OR of non-response in patients with angina.			0.9, (0.1, 8.0), p= 0.944.
	OR of non-response in patients who have had a stroke or TIA.			0.0 p= 0.999.

	OR of non-response in patients who have smoked >20 pack years.			2.3 (0.8, 6.7), p= 0.123.
	OR of non-response in patients with BMI >30kg/m2.			1.4, (0.5, 3.8), p= 0.566.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	OR of non-response in patients with lesion type occult CNV.			1.0, p= 0.177
	OR of non-response in patients with lesion type RAP			1.1, (0.2, 4.9), p= 0.945.
	OR of non-response patients with lesion type predominantly classic			1.8, (0.8, 4.0), p= 0.156.
	OR of non-response in patients with lesion type minimally classic			2.5, (1.0, 6.2), p= 0.05.

	OR of non-response in patients with lesion size <2 DA			<2 DA: 1.0, p= 0.058.
	OR of non-response in patients with lesion size 2- 4 DA			2.8, (1.0, 7.6), p= 0.045.

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	OR of non-response in patients with lesion size >6 DA			3.9, (1.3, 11.0), p= 0.011.
	OR of non-response in patients of age >80 years			2.2 (1.2, 4.1), p= 0.012.
	OR of non-response in patients with baseline VA 1.>20/63, 2. 20/63-20/200, 3. 20/200-20/640, 4. ≥ 640			VA: 1. 1.0 p= <0.001. 2. 3.3 (1.3, 8.0), p= 0.009. 3. 3.8, (1.5, 9.9), p= 0.006. 4. 30.4, (7.0, 133.0), p=

				<0.001.
	OR of non-response in patients with diabetes			Diabetes: 3.1 (1.3, 7.3), p= 0.009.
Ying *et al.*, (2015)	OR for ≥3-line gain from baseline at 1 year in patients aged 50-69, 70- 79, 80-89, ≥90	Age, VA, area of CNV, geographic atrophy, RAP lesion, RPE elevation.	None.	50-69: 1.00 70-79: 0.62 (0.37, 1.02) 80-89: 0.44 (0.27, 0.73) ≥90: 0.67 (0.32, 1.41)

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
				P= 0.008
	OR for >3-line gain from baseline at 1 year in study eye of patients with baseline VA 68-82, 53-67, 53-67, 38-52, 23-37 letters			68-82: 0.11 (0.07, 0.18) 53-67: 1.00 38-52: 2.60 (1.80, 3.77) 23-37: 1.73 (0.97, 2.07)

				P= <0.0001
	OR of ≥3-letter gain from baseline to year 1 in fellow eye of patients with baseline VA 83-100, 68- 82, 0-67 letters			83-100: 1.00 68-82: 0.90 (0.63, 1.30) 0-67: 0.53 (0.35, 0.80) P= 0.005
	OR of ≥3-letter gain from baseline to year 1 in patients with baseline area of CNV (mm2) ≥2.54, >2.54 to ≤5.08, >5.08 to			≥2.54: 1.00 >2.54 to ≤5.08: 0.71 (0.47, 1.07)

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	≤10.2, >10.2, cannot measure			>5.08 to ≤10.2: 0.67 (0.38, 1.18) Cannot measure: 0.44 (0.25, 0.76) P= 0.04

	OR of ≥3-letter gain from baseline to year 1 in patients with and without RAP lesion			No RAP lesion: 1.00 RAP lesion: 1.94 (1.21, 3.10) P= 0.004
	OR of ≥3-letter gain from baseline to year 1 in patients with total foveal (um) thickness of 3. 1st quartile (≤325) 4. 2nd quartile (>325 to <425)			1. 1.00 2. 1.74 (1.11, 2.72) 3. 1.15 (0.73, 1.82) 4. 0.80 (0.50, 1.27)

Study	Outcome	Demographic Factors Investigated	Clinical Factors Investigated	Outcome
	3. 3rd quartile (>425 to ≤550) 4. 4th quartile (>550)			
	OR of ≥3-letter gain from baseline to year 1 in patients with and without RPE elevation at baseline			No RPE: 1.00 RPE: 0.52 (0.34, 0.79)

				P= 0.002
	OR of ≥3-letter gain from baseline to year 1 in patients treated with 1. ranibizumab monthly 2. ranibizumab PRN 3. bevacizumab monthly 4. bevacizumab PRN			1. 1.00 2. 0.80 (0.53, 1.22) 3. 0.56 (0.37, 0.86) 4. 0.63 (0.41, 0.96) P= 0.04

VA= visual acuity.

ETDRS= Early Treatment Diabetic Retinopathy Study CRT= central retinal thickness

SD= standard deviation

***= significance level set at <0.0029**

****= significance level set at <0.20 OR= odds ratio**

BCVA= best corrected visual acuity CNV= choroidal neovascularisation DA= disc area

FFA= fundus fluorescein angiography frontal fibrosing alopecia CFT= central foveal thickness

SRF= sub-retinal fluid.

ORT= outer retinal tabulation HF= hyperreflective foci ERM= epiretinal membrane IRF- intra-retinal fluid

PED= pigment epithelial detachment IS junction= inner segment junction OS= outer segment junction

ELM= external limiting membrane

LD= loading dose

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