Aspects of quality of life in the patient journey in glaucoma

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List of Abbreviations

AGC: Aberdeen Glaucoma Questionnaire

AIC: Akaike Information Criterion

AS: Anterior Segment

VEGF: Vascular Endothelial Growth Factor

ALT: Argon Laser Trabeculoplasty

AFREV: Assessment of Function Related to Vision

BEMD: Best Eye Mean Deviation

BMJ: British Medical Journal

CAI: Carbonic Anhydrase Inhibitor

CI: Confidence Interval

COREQ: Consolidated Criteria for Reporting Qualitative Research

dB: Decibels

EMGT: Early Manifest Glaucoma Trial

EGS: European Glaucoma Society

EQ-5D: European Quality of Life in 5 dimensions

GAL-9: Glaucoma Activity Limitation

GHT: Glaucoma Hemifield Test

GMS: Glaucoma Monitoring Service

GQL-15: Glaucoma Quality of Life

GAT: Goldmann Applanation Tonometry

HES: Hospital Eye Service

HFA: Humphrey Field Analyser

IT: Information Technology

IQR: Interquartile Range; IQR

IOP: Intraocular Pressure

JOAG: Juvenile Open Angle Glaucoma,

MD: Mean Deviation

MMC: Mitomycin C

NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

OHT: Ocular Hypertension

OCT: Optical Coherence Tomography

OLSR: Ordinary Least Squares Regression

PROM: Patient-Reported Outcome Measure

PDF: Portable Document Format

PSD: Pattern Standard Deviation

PCG: Primary Congenital Glaucoma,

POAG: Primary Open Angle Glaucoma

RNFL: Retinal Nerve Fibre Layer

RNIB: Royal National Institute of the Blind

SACG: Secondary Angle Closure Glaucoma

SLT: Selective Laser Trabeculoplasty

SF-36: Short-Form Health Survey

SITA: Swedish Interactive Testing Algorithm

SOAG: Secondary Open Angle Glaucoma

UK: United Kingdom

UKGTS: United Kingdom Glaucoma Treatment Study

VA: Visual Acuity

VAS: Visual Analogue Scale

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Declaration

The work contained in this thesis was completed by the candidate, Lee Jones (LJ), under the supervision of Professor David Crabb. It has not been submitted for any other degrees, either now or in the past. Where work contained within this thesis has been published previously, this has been stated in the text. All sources of information have been acknowledged and the appropriate references have been given. The University Librarian of City, University of London is permitted to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers single copies made for study purposes, subject to normal conditions of acknowledgement.

Abstract

Open angle glaucoma is a chronic disease of the optic nerve, where damage to the visual field can result in loss of vision. There is currently no cure for the disease. The four studies presented within this thesis aimed to explore aspects of the impact of glaucoma on patients' everyday living and quality of life. The studies were designed to capture aspects of the 'journey' in glaucoma which may be particularly challenging for the patient; the initial stage, where quality of life may be reduced and the accompanying burden of ongoing disease monitoring; and the end stage, where significant loss of vision will likely cause visual disability and the daunting prospect of undergoing high-stakes ocular surgery. In the first study, the relationship between visual field loss (measured using mean deviation [MD]) and vison-related quality of life was assessed. Evidence indicated that glaucoma has a negative impact on vision-related quality of life, even in the earliest stage of the disease. However, the relationship is likely to be non-linear, as certain phases of the disease are more likely to have a greater impact than others. Specifically, each 1 decibel reduction in MD was associated with a decline of 2.3 (out of 100) units on a quality of life metric in the early stage of glaucoma ($p<0.001$), and 4.6 units in advanced disease ($p=0.009$). In the second study, vision-related quality of life was assessed amongst a cohort of newly-diagnosed glaucoma patients taking part in a randomised glaucoma therapy clinical trial. Responses on patient-reported outcome measures (PROMs) were assessed for group differences between treatment arms of the trial. In addition, group differences in quality of life between the stable patients and those with glaucomatous progression was compared. There were no statistically significant differences on PROMs between the two trial arms. Differences between stable and progressing glaucoma patients were observed only on PROMs specific to glaucoma (Glaucoma Quality of Life-15, $p = 0.02$; Glaucoma Activity Limitation-9, $p = 0.02$). In the third study, the equivalence of visual field measurement outcomes were assessed between patients attending standard glaucoma care services and those attending a novel glaucoma service, a virtual clinic. Average MD measurements for 250 patients in the virtual clinic were compared with a 'big data' repository of patients in the standard glaucoma service, which was used to calculate expected MD values. The speed of visual field progression between the two groups was also assessed. In the first analysis, 12 (4.8%; 95% confidence interval 2.5% to 8.2%) virtual clinic patients scored outside the 90% expected values based on the big data repository. In the second analysis, 1.9% (95% confidence interval 0.4% to 5.4%) virtual clinic patients had visual field changes outside of the expected 90% limits. In the fourth study, patient and surgeon experiences of advanced glaucoma surgery were assessed in a qualitative analysis. Interview transcripts underwent thematic analysis where, for the patients, key emerging themes included the emotional impact surgery, developing coping mechanisms, and how to improve the patient's surgical journey. For the surgeons, themes included strategies for risk reduction, views on training, and the emotional impact of performing surgery on advanced glaucoma patients. To conclude, these studies highlight aspects of the patient journey in glaucoma where the disease may be most burdensome and troubling for the patient. Some practical changes, such as performing monitoring measurements in a virtual clinic, or augmented surgical care services for patients with advanced disease may help to ease the burden of glaucoma. In addition, the findings from these studies can help to improve understanding of the glaucoma journey and serve as an effective resource for learning, support, and professional development for patients, relatives, and carers, as well as professionals specialising in eye care.

Chapter One - Introduction

The aim of this PhD is to investigate the patient experience of glaucoma and its impact on quality of life. Specifically, the purpose was to assess three key patient-centred aspects of the disease; measuring, monitoring, and treatment. In order to clarify the aims for this work, this chapter gives a summary of relevant background literature. Further details of the specific aims of the PhD are outlined at the end of this chapter.

1.1 Glaucoma definition and epidemiology

Glaucoma refers to a group of conditions whereby the optic nerve head and retinal ganglion cells are progressively damaged, causing loss of vision. Damage caused by glaucoma is irreversible, and the disease is the leading cause of blindness in the world (King et al., 2013). The number of people living with glaucoma worldwide is estimated to be 64 million, and this figure is expected to rise to 76 million by 2020 (Tham et al., 2014). Glaucoma affects approximately 3% of the worldwide population aged between 40 and 80 years, and these estimates rise as age increases (Khawaja et al., 2013). In the United Kingdom, life expectancy is increasing (Office for National Statistics, 2011), thus glaucoma is set to become a significant burden on the hospital eye services. Indeed, treatment can slow glaucomatous vision loss (Heijl et al., 2002), therefore early detection is crucial to preserve visual function (Oliver et al., 2002). However, it is predicted that many individuals living with glaucoma remain undiagnosed in developed countries, with estimates ranging from 30-50% (Shaikh et al., 2014; Chan et al., 2017).

1.2 Glaucoma risk factors

Primary open angle glaucoma (POAG) is the most prevalent form of glaucoma, and the data collected and utilised in this thesis relate to this variant of the disease. There are a number of risk factors in glaucoma, however the only modifiable of these is intraocular pressure (IOP) (Crabb, 2016). A person's IOP is determined by the rate of aqueous (watery fluid located in the anterior and posterior chambers of the eye) secretion and the rate of outflow via the trabecular meshwork. Aqueous outflow is dependent on the presence of resistance at the point of the eye's outflow channels. In POAG, there is typically an insufficient outflow of aqueous and an increase in IOP. At this point it is important to note that not all individuals with high levels of IOP have glaucoma, but rather these patients are referred to as having ocular hypertension (OHT). Similarly, not all glaucoma patients have high IOP, as in the case of normal tension glaucoma. Yet, high levels of IOP

have repeatedly been evidenced as risk factor for glaucoma (Gordon et al., 2002; Chauhan et al., 2008), and IOP is known to influence disease progression in glaucoma (Heijl et al., 2012; Garway-Heath et al., 2015). There are various other risk factors for glaucoma including, but not limited to, aging (Leske et al., 2007), family history of the disease (Coleman & Miglior, 2008), and ethnicity, where African-Caribbean individuals are significantly more likely to develop POAG, with a much earlier onset in this population (Racette et al., 2003).

1.3 Glaucoma pathophysiology

Glaucoma can cause a reduction in both peripheral and central visual sensitivity. The reduction in sensitivity is attributed to the premature death of ganglion cells located in the retina (Casson et al., 2012). In order to understand the significance of this damage, it is necessary to consider the anatomy of the eye and the process of visual perception. Briefly, light enters the eye through the cornea and travels to the retina at the back of the eye, where it progresses through layers of cells before reaching the photoreceptors. The photoreceptor cells, known as rods and cones, are activated at low and high levels of luminance, respectively. In other words, rod cells are responsible for scotopic vision and cone cells for photopic vision, and therefore collectively allow the visual system to process information at all light intensities. Signals received by the photoreceptor cells are communicated toward the axons of the retinal ganglion cells. These axons cover the whole area of the retina and are collectively referred to as the retinal nerve fibre layer. The retinal ganglion cells allow for the transmission of information from the photoreceptors towards the brain via the optic nerve head. However, when the retinal ganglion cells become damaged, as with glaucoma, signals cannot effectively be transmitted to the optic nerve and brain, resulting in reduced visual sensitivity.

The result of damaged retinal ganglion cells in glaucoma can lead to patches of poor vision where the brain receives no information. The patches are referred to as scotomas. Scotomas are regions of vision loss, or areas of an individual's visual field which is not apparent, or which are 'missing'. Individuals with glaucoma do not perceive their vision loss as a black tunnel or areas of perceptive blackout; rather, these areas are more likely to be described as blurry or missing regions, see Figure 1.1 (Crabb et al., 2013). Hence patients are typically unaware of glaucomatous vision loss in the early stages of the disease. Yet, many studies note that glaucoma patients report greater difficulty with

visually demanding tasks as the severity of their glaucoma increases (Ramulu, 2009; Jampel et al., 2002; van Gestel et al., 2010; McKean-Cowdin et al., 2008). These findings suggest that as glaucoma progresses and becomes more advanced, vision loss may become more perceptible to the patient. However, as the visual fields of both eyes overlap, normal vision in one eye may compensate for a defect in the affected eye, resulting in the visual loss being unnoticeable for the patient (Safran & Landis, 1999). This phenomenon, referred to as 'filling-in', can explain why glaucomatous visual field loss may only begin to affect patients' activities when the disease is quite advanced and vision loss is bilateral (Crossland & Rubin, 2007).

Figure 1.1: Images used to portray commonly used simulations of the point-of-view of an individual with glaucomatous vision loss. Percentages given [%] refer to the proportion of respondents (N=50) stating the depiction is representative of their vision. A: Black tunnel [0%], B: blurred tunnel [4%], C: black patches [0%], D: blurred patches [54%], E: missing parts [16%], and F: no difference [26%]. (Crabb et al., 2013).

1.4 Detecting and monitoring glaucoma

The onset of glaucoma is insidious as the patient is typically unaware they have the disease in its early stages. Often, glaucoma is detected through opportunistic case finding during patients' routine examination at their local optometrist (Lawrenson, 2013), where patients are then typically referred into the hospital eye service for evaluation (Bowling et al., 2005). Diagnostic evaluation consists of examination of the anterior chamber angle, the reference standard for which is gonioscopy, measurement of IOP via tonometry, imaging of the optic discs, and visual field testing (Tuulonen et al., 2003). Once diagnosed, glaucoma requires lifelong monitoring, and this is typically carried out in secondary care. IOP is monitored and any changes to visual function are assessed through visual field testing. Structural changes to the eye are assessed via photography and scanning technologies, such as fundus photography and optical coherence tomography (OCT). The decision regarding how often patients' glaucoma should be evaluated typically depend on the severity of the disease and the patient's age. Stable glaucoma (usually defined as unchanged visual field and IOP within target range) is considered low clinic risk and is typically reassessed every twelve to eighteen months, while advanced or progressing glaucoma is monitored more closely, with clinic visits scheduled approximately every one to six months until stable, depending on certainty of progression and control of IOP (The Royal College of Ophthalmologists, 2016; NICE, 2017). Yet, determining glaucomatous progression is challenging due to measurement variability (Henson et al., 2000; Sultan et al., 2009), thus several clinic visits are usually required in order to assess disease progression.

1.4.1 Gonioscopy

Gonioscopy is used to assess the structure of the angle of the anterior chamber. The configuration of the angle is used to determine the type of glaucoma, where a wide angle is indicative of POAG. Conversely, a narrow angle is associated with angle closure glaucoma. In POAG, gonioscopy is used to monitor the width of the angle and a numerical grade can be assigned.

1.4.2 Tonometry

Tonometry is the objective assessment of IOP. Whilst elevated IOP is not always synonymous with glaucoma, it remains the only modifiable risk factor. As such, tonometry is pivotal in the monitoring of glaucomatous progression. Tonometry assessment measures the amount of force required in order to compress a small area of the cornea and reports the pressure reading in terms of millimetres of mercury (mmHg). The reference standard for tonometry is Goldmann applanation tonometry (GAT) (Wessels & Oh, 1990). GAT is an example of contact tonometry whereby a small probe is used to acquire an IOP reading. Other forms of tonometry include non-contact and rebound methods, both of which do not require anaesthesia, the former relying on a jet of air, and the latter using a bouncing probe to measure IOP. Central corneal thickness has the potential to bias tonometry measurements which can result in overestimations or underestimations of IOP levels (Copt et al., 1999). As such, it is not recommended to rely solely on tonometry when assessing disease progression in glaucoma.

1.4.3 Fundus photography

Assessment of the fundus (optic nerve head; retina; and blood vessels) is essential when monitoring the health of the eye. Changes in the appearance of the optic nerve can often occur prior to any loss of vision observed in glaucoma. As such, assessment of the optic nerve head is valuable for diagnosing glaucoma, particularly in the early stages of the disease (Weinreb & Khaw, 2004). The optic nerve head is visualised through opthalmoscopic examination (direct or slit-lamp biomicroscopy methods), or digital fundus photography. During examination, the assessor will estimate the amount of nerve tissue that is present at the optic nerve head, such as by calculating the cup-to-disc ratio (Quigley et al., 1992), where the cup is located in the centre of the disc shape of the optic nerve head. A cup-to-disc ratio of 0.3 (the cup occupies a third of the height of the entire disc) is generally considered healthy, and an increased cup-to-disc ratio may indicate glaucomatous damage. The usefulness of fundus assessment is dependent on observer skills, where there is often high inter-observer and intra-observer variation (Gaasterland et al., 2001).

1.4.4 Optical coherence tomography

Optical Coherence Tomography (OCT) is a non-invasive imaging system which provides high resolution cross-sectional images of different parts of the eye, including the retina and optic nerve. OCT can provide important information regarding the presence of glaucoma by examining the retinal nerve fibre layer (RNFL). The RNFL will be relatively thick in a healthy eye, and the detection of 'thinning' may be indicative of glaucoma (Quigley, 2011). Yet, a valid determination of changing RNFL requires an accurate baseline measurement against which future measurements can be compared. This can sometimes be challenging as factors including older age, poor best-corrected VA, greater degree of myopia, and presence of cataracts have been associated with reduced signal strength in OCT which may impact the validity of the image (Lee et al., 2018).

1.4.5 Visual fields

The visual field test is used to detect defects in the central and peripheral areas of vision, thus, is a vital component to glaucoma diagnosis and monitoring. The visual field is defined as the area where light reaches the retina and stimulates the photoreceptors, which transmit electrical signals to the brain via the retinal ganglion cells (Werner 1991; Henson, 2000). The functionality of the visual field is assessed using perimetry. The Humphrey Field Analyser (HFA; Carl Zeiss Meditec, Dublin, CA) is considered the gold standard for performing perimetry (Beck et al., 1985). When using the HFA, the individual is required to place their head onto the chin support facing into the machine. A small light stimuli will then be presented at various locations which correspond to different locations on the retina. The individual is asked to fixate at the central point and respond each time they see the light stimuli by pressing a button. The test is usually performed monocularly, where one eye will be occluded. There are a number of different testing patterns, such as the 10-2 and 30-2, but the 24-2 is usually the most common. Put simply, the '24' refers to the fact this test is measuring the visual field extending out to 24° from the central fixation point in all four directions (thus, the central 48° of the visual field). The second number, the '2', indicates that the test is the second variation of the testing pattern (now routinely used over the previous patterns, i.e. 24-1). Defects within the visual field are identified if light sensitivity at a specific location is below the average sensitivity that would be recorded by a person of a similar age with healthy vision, known as age-matched controls. Information generated in the visual field test is summarised into a

number of 'global indices' which are reported on the output created by the machine (Figure 1.2). One such output is the mean deviation (MD), which indicates how much, on average, the individual's visual field sensitivity deviates from the age-matched normal, and is reported in decibels (dB). In research, it is common to use the MD as a metric for assessing how glaucomatous the individual's visual field appears to be. Lower scores are indicative of greater damage to the visual field. For example, one crude method is to use dB bins of: better than -6dB, between -6dB and -12dB, and worse than -12dB for early, moderate, and advanced glaucoma, respectively. These MD groupings will often be corroborated by other clinical measurements (Kotecha et al., 2015a). This thesis will primarily use visual field MD as a metric for assessing glaucoma severity. Another metric provided by HFA is the pattern standard deviation (PSD), which gives information about localised vision loss. This is useful as the presence of cataracts can result in misleading visual field outputs (e.g. cataracts cause the eye's lens to become opaque leading to excessive light scatter which the PSD metric can account for by correcting for overall depression in light sensitivity (King et al., 2013)). The HFA output also provides displays which offer valuable information about the functionality of the visual field, such as the numerical display giving the threshold for all points of the visual field. These are referred to as the point-wise visual field data and can provide sensitive estimates of visual function (Bryan et al., 2013). The visual field greyscale image offers a simpler means of interpreting the test results, whereby decreasing sensitivity is represented by darker tones. It is important when assessing visual field results to take into account the reliability indices as these will reflect the extent to which the patient's results are reliable and therefore should be analysed first. Fixation losses, false positives, and false negatives are used to assess reliability, and unreliable measurements may require repeat testing.

The visual field test can be time-consuming and challenging for the patient to complete (Glen et al., 2014). This can be problematic as fatigue and learning effects are likely to impact the reliability of the measurements (Heijl & Bengtsson, 1996). Fatigue may artifactually decrease visual field sensitivity estimates, whereas learning effects may result in improved sensitivity between examinations. The latter can be explained by the patient being unfamiliar with the visual field testing method in their first attempt at performing perimetry. This is often remedied by excluding the first recorded visual field from analyses (Artes et al., 2005).

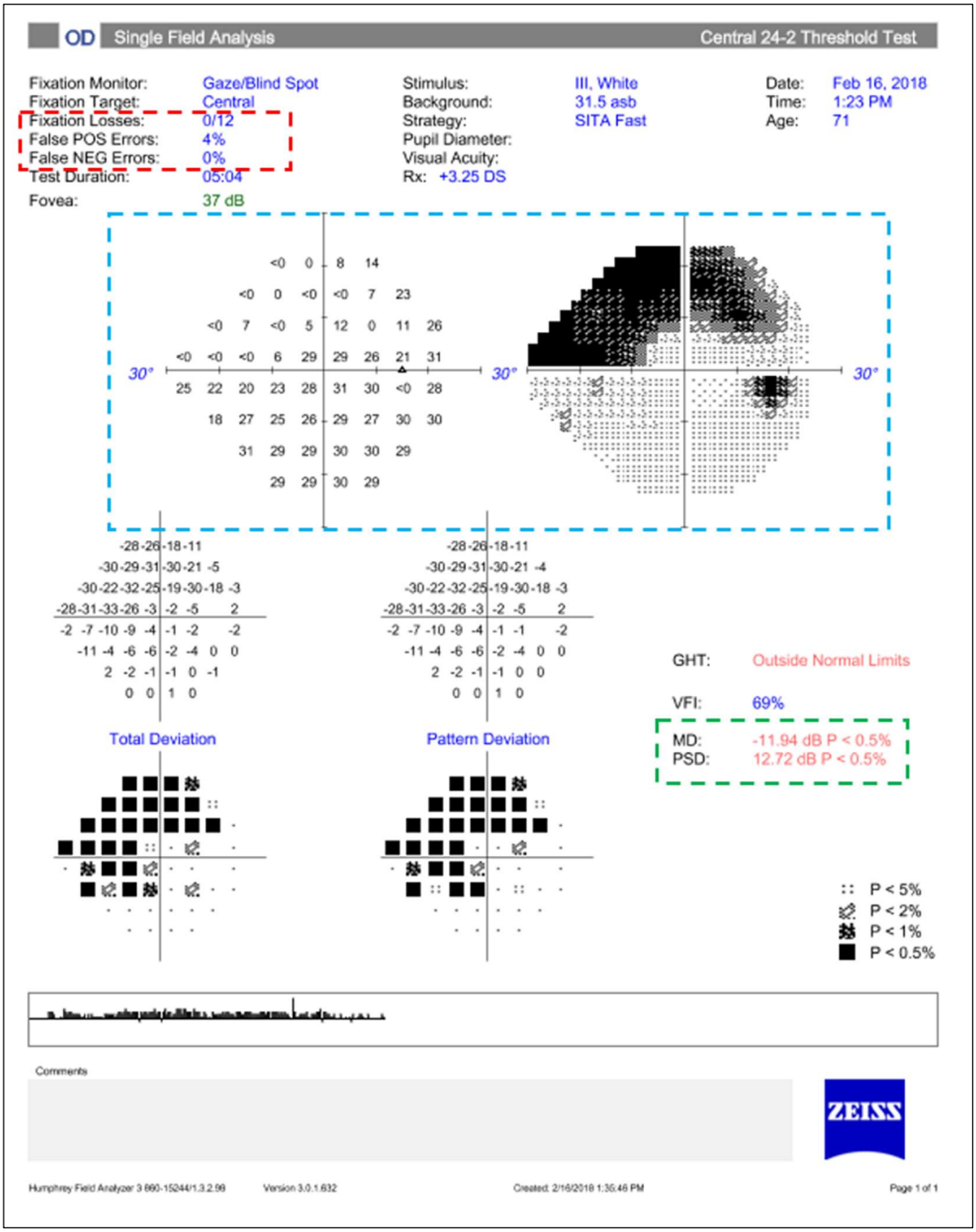

Figure 1.2: An anonymised HFA output portraying a visual field produced by a right eye. The measurement is indicative of a superior arcuate defect. Fixation losses, false positives and false negatives are indicated in the top left. Outlined red are the reliability indices, outlined blue are the numerical and greyscale displays, outlined green are the MD and PSD global indices.

1.4.6 The burden of monitoring glaucoma

Glaucoma patients require lifelong monitoring and this can consume patients' time and other resources. Patients can expect their hospital visits to take up to three hours, not

including transport time (Kotecha et al., 2015a). The duration of appointments can impact glaucoma patients financially, whereby costs of travel to the hospital, as well as loss of income due to absenteeism from work can negatively affect quality of life (Kong et al., 2014). In addition, patients are often accompanied on their hospital visits by a family member or care provider (Sharma et al., 2010), which may result in the patient having feelings of being a burden, potentially causing further repercussions for quality of life. A recent report from the Royal National Institute of the Blind (RNIB) stated that a primary concern for glaucoma patients was the long delays experienced in the hospital eye services, citing a fear that such delays can result in disease progression and loss of vision (RNIB, 2013). Novel services aimed to combat long clinic visits and waiting times have been implemented, such as virtual glaucoma monitoring, and are described further in the following section.

1.4.7 Virtual glaucoma clinics

One resolution for long hospital waiting periods is the implementation of virtual glaucoma clinics in the hospital eye service. Virtual clinics allow for rapid testing whereby nurses or ophthalmic technicians collect clinical data from the patients in a streamlined fashion, often from a sole clinic room, for a consultant ophthalmologist or a delegated glaucoma reviewer to review at a later time (Figure 1.3). The patients are then informed of their results approximately one week later via email or telephone, as preferred.

Figure 1.3: Layout of a virtual glaucoma monitoring system where patients perform clinical testing at a number of relevant stations. Image taken from Digital Health and Care Congress, 2017, The King's Fund. (https://www.kingsfund.org.uk/sites/default/files/media/Aachal_Kotecha.pdf).

Patients who are monitored in a virtual glaucoma clinic are those who are deemed suitable for the service at the discretion of their referring consultant. Standards for virtual clinics in glaucoma care in the National Health Service (NHS) hospital eye service suggest this method of monitoring may be suitable for patients with OHT, suspected open angle glaucoma, or early/moderate primary open angle glaucoma in the worse eye (The Royal College of Ophthalmologists, 2016).

The virtual glaucoma clinic service has been found to improve in-patient capacity and streamline referral rates (Kotecha et al., 2015a). A virtual service has the potential to improve aspects of quality of life in glaucoma patients, too. For example, the average visit to the virtual clinic is less than one hour, compared to three hours in standard care (Kotecha et al., 2015b). As a result, the carer burden will likely be lower for virtual clinic patients compared to patients in the standard service, as appointments would be significantly shorter. In addition, transportation and parking fees have been ranked as high cost outgoings for patients in hospital-based glaucoma care (Sharma et al., 2010). Hospital parking fees for patients have increased (Rye & Ison, 2005), and shorter visits will benefit regular hospital attendees financially. Evidence suggests that patients are generally accepting of having their glaucoma monitored in a virtual service, as long as they are kept well informed and believe that the staff working in the clinic are suitably competent (Kotecha et al., 2015b). Yet, it is important to consider that a virtual service may not be appropriate for all patients, including those who fit the virtual clinic eligibility criteria. Patients may report feelings of discomfort about the fact they do not come into direct contact with a doctor while at a virtual clinic appointment, which may subsequently increase patient anxiety (Kotecha et al., 2015b). Furthermore, while virtual clinics are designed to support a more streamlined service, evidence suggests that this method of monitoring is less cost-effective than standard services due to greater clinic re-attendances often required (Jones et al., 2018).

It is important to consider whether the virtual glaucoma service is a viable means of monitoring patients, and this is investigated further in this thesis (see Chapter 4). Although no quality of life metrics were used in this study, the idea was to explore whether patients whose glaucoma is no longer stable, and so requiring closer observation, are effectively identified by clinic staff. The results of the study can have significant implications for the way in which glaucoma patients are monitored in the hospital eye service, and consequently affecting patient quality of life.

1.5 Treatment of glaucoma

Management of IOP can slow glaucomatous retinal ganglion cell damage. A number of well-designed clinical trials have demonstrated the vision-preserving benefit of reducing IOP in patients with glaucoma and ocular hypertension (Kass et al., 2002; Heijl et al., 2002; Garway-Heath et al., 2015). There are several methods which may be employed to reduce patients' IOP, the first line treatment typically being eye drops. The decision to begin topical treatment should not be taken lightly. In most cases, initiation of treatment commits the patient to lifelong therapy, or until the treatment becomes ineffective. In addition, treatment can often lead to side effects, such as ocular surface discomfort, which may significantly affect the day-to-day life of the patient (Schweitzer et al., 2001; Nordmann et al., 2003; Skalicky et al., 2012). The decision of whether or not to initiate treatment is often based on how aggressive the disease is, i.e. is glaucomatous damage progressing rapidly or slowly for the patient. In cases of very slowly progressive disease, patients may not be prescribed eye drops immediately so that they are not unnecessarily exposed to the side effects, costs, and inconvenience that are associated with glaucoma treatment. On the other hand, treatment should not be delayed for patients who are at high risk of glaucomatous progression. The Ocular Hypertension Treatment Study (Kass et al., 2002) evidenced that topical medications can delay the onset of glaucoma in patients with elevated IOP. However, the authors note these results should not imply that all patients with elevated IOP should be treated with hypotensive medication. Rather, the decision to recommend treatment should consider many factors, such as the burden of long term treatment, the individual's likelihood of being helped by treatment, the individual's health status, and the fact that the overall incidence of patients with elevated IOP developing glaucoma is low (Gordon et al., 2002).

1.5.1 Medical Therapy

Most glaucoma medications are administered topically and in the form of eye drops. Glaucoma eye drops are hypotensive agents which aim to reduce IOP. As a general rule, one medication will be prescribed with the aim to achieve a target IOP which is set by the patient's clinician.

Prostaglandin Analogue: The most widely used anti-glaucoma medications are prostaglandin analogues, which aim to increase aqueous outflow away from the eye (McKee et al., 2005). Common prostaglandin analogues include Latanoprost, Travoprost,

and Bimatoprost. Prostaglandin analogues are the preferred choice for most patients due to the fact they need to be administered only once per day (Li et al., 2006). However, there are a number of ocular side effects associated with the use of these medications, including irritation, foreign body sensation, increased pigmentation, and longer eyelashes. Systemic side effects of prostaglandin analogues can include occasional headache and upper respiratory tract symptoms, such as coughing and sneezing.

Beta-Adrenergic Agonists: Beta-blockers may also be prescribed as an anti-glaucoma medication. The most frequently used Beta-blocker in glaucoma care is Timolol which aims to lower IOP by reducing aqueous secretion. Beta-blockers are often more effective when prescribed as an adjunct to, or in combination with prostaglandin analogues. Use of Beta-blockers has been shown to correlate with exacerbated breathlessness which can be problematic for individuals with asthma or chronic obstructive pulmonary disease (Diggory et al., 1995). In addition, prolonged usage of Beta-blockers has been associated with mood alterations, decreased libido, and impotence (Shore et al., 1987). Moreover, these side effects are likely more common than acknowledged as it is not typical for ophthalmologists to ask patients about such systemic side effects, and patients may not associate them with their medication (Stamper, 2002).

Carbonic Anhydrase Inhibitors: These topical medications, such as Dorzolamide decrease IOP by reducing the formulation of aqueous. Although slightly less effective than Beta-blockers, Carbonic Anhydrase Inhibitors (CAI) are often preferred due to being well tolerated by patients (Balfour & Wilde, 1997). When used on their own, CAIs may require three-times daily dosing (Stamper, 2002) which can result in poor adherence to medication (Gurwitz et al., 1993). Serious side effects associated with CAIs are rare, but episodes of hypotony and choroidal detachment have been documented (Fineman et al., 1996).

Alpha-Adrenergic Agonists: Such agents as Brimonidine are potent IOP lowering medications with similar efficacy to Timolol (Katz, 1999). Alpha Agonists attempt to lower IOP by both increasing aqueous outflow and decreasing its formation. The medication is usually most effective at twice-daily dosing, and in some cases, three-times-per-day. Drowsiness, dry mouth, headache, and dizziness are uncommon but potentially

significant side effects associated with Brimonidine (Javitt & Goldberg, 2000; Stamper, 2002).

Non-adherence to topical medication is a concern in glaucoma treatment. There are a number of factors which can lead to non-adherence, including high frequency of treatment administration (2+ administrations per day) and the presence of multiple other medications in the patient's therapy regimen (Gurwitz et al., 1993). In addition, glaucoma patients often do not perceive any vision loss, especially in the early stages of the disease, and so do not consider medication adherence to be necessary, or the patient does not fully understand their diagnosis of glaucoma, or how to correctly use their medication (Shaw, 2005). There are a number of strategies that can be employed to improve medication adherence, such as introducing a simpler treatment regimen, combination treatments if more than one drug is required, effective communication and encouragement regarding the importance of regular treatment, and regular review and reassurance to the patient. Educating patients about their disease can be an inexpensive means of maintaining high medication adherence (Cate et al., 2014). Moreover, those who are most at risk of glaucoma, i.e. the elderly population, can also suffer with problems regarding dexterity, such as arthritis, which can make successful administration of drops particularly challenging.

1.5.2 Laser Therapy

There are a number of different laser treatments available that aim to lower IOP. The selective laser trabeculoplasty (SLT) is a routinely used treatment in which the laser is directed to the trabecular meshwork (Latina & Tumbocon, 2002). The SLT is considered a safer option over the previous gold standard, Argon laser trabeculoplasty (ALT), mainly due to the fact SLT can specifically target cells that require treatment within the trabecular meshwork (melanin pigment is targeted while non-pigmented cells and structures are unscathed). SLT can enhance trabecular outflow (Kagan et al., 2014; Leahy & White, 2015) which in turn, reduces IOP. The procedure can provide sustained IOP reduction for a number of years. As a result, there is less of a dependence on topical medications and this may preserve the integrity of the ocular surface. Research surrounding the use of SLT as opposed to Latanoprost as a first-line treatment for glaucoma suggests medical therapy may have a greater success rate than laser therapy (Nagar et al., 2005). Yet, SLT has the benefit of usually being a one-time intervention which does not require patient

adherence as with medical therapy. Laser therapy is relatively quick to perform and does not require general anaesthetic. The procedure is usually then implemented if topical medications are ineffective, or when patients are unable to adhere or tolerate the side effects of ocular drops. Laser therapy has been evidenced as an effective means of lowering IOP when first line medications have been ineffective (Juzych et al., 2004; Heijl et al. 2002). In addition to ALT and SLT, aggressive laser therapies may be used in cases where IOP remains uncontrollable. Cyclodestructive procedures, such as Cyclodiode laser ablation, lower IOP through the part-destruction of the ciliary body to reduce aqueous secretion. Cyclodiode laser therapy can be successful in providing pain relief in advanced glaucomatous eyes with very high IOP (Martin & Broadway, 2001).

1.5.3 Surgery

Surgical intervention is often the final line of treatment for glaucoma. That is, surgery is usually opted for after topical and laser therapies have not achieved the desired results. For patients with severe glaucomatous damage, or those who are poorly adherent to medications, surgery may be offered as a first line treatment. Trabeculectomy is the most commonly performed incisional glaucoma surgery to lower IOP (Figure 1.4). The surgery consists of a small incision in the trabecular meshwork and adjacent tissue to provide a drainage route for the aqueous fluid to leave the eye. Scarring during the healing process can cause this route to close resulting in a re-increase in IOP. Mitomycin C (MMC) is applied during the surgical procedure which helps to prevent scarring by inhibiting the growth of cells which are responsible for the production of scar tissue (Khaw et al., 1992). Injections of anti-scarring agents, such as antivascular endothelial growth factor (Anti-VEGF), can be applied to the surgical site during post-operative care to increase the success rate of surgery (Zhongqui et al., 2009). However, these injections can also increase the rate of complications and the long-term effects of usage have yet to be realised (Slabaugh & Salim, 2017). Alternative forms of surgical intervention are available, such as artificial tubular drainage implants, which attempt to regulate aqueous outflow to reduce IOP. This intervention is considered particularly invasive and expensive and, thus, are usually prescribed when an aggressive approach to treatment is required, or when previous interventions have been unsuccessful (NICE, 2009).

Figure 1.4: An image of a flap valve being created to allow aqueous outflow in a trabeculectomy procedure. Image taken from International Ophthalmology Portal (http://iop.vision).

Researchers have recognised the unique impact ophthalmic surgery can have on patients' psychological wellbeing. However, such studies are mainly orientated towards the emotional impact of cataract surgery on patients with binocular vision (Nijkamp et al., 2004; Marback et al., 2007). In a study comparing patients with binocular or monocular vision undergoing cataract surgery, individuals who had only one eye reported greater fear of surgery, citing blindness, worsened vision, and surgical complications as their primary concerns (Marback et al., 2012). Furthermore, fear of blindness following trabeculectomy has been reported in patients with advanced bilateral glaucoma (Cross et al., 2009), and even in patients with early glaucoma and fairly good binocular vision (Janz et al., 2001). Yet, there appear to be no studies to date which specifically focus on the experiences of glaucoma patients undergoing surgery on their one only-seeing eye (Figure 1.5). This advanced glaucoma 'only-eye' population represents a unique group of patients in the hospital eye service who have experienced unprecedented challenges in their treatment journey, such as loss of vision monocularly, usually multiple failed interventions, and numerous surgical procedures. These patients can provide insight into experiences of late-stage glaucoma and surgical intervention which can be used as an important resource for professional development and patient education. This idea is explored further in a qualitative study described in Chapter 5 of this thesis.

Figure 1.5: A painting from the educational project entitled 'Prize your Eyes' whereby schoolchildren were asked to reflect on the causes and impact of major eye trauma – one of which being an illustration of monocular or 'only-eyed' vision. Image courtesy of Professor Peter Shah (personal communication).

1.6 Vision-related quality of life

Quality of life is a broad and multifaceted concept. It can be described as the sense of personal satisfaction with the conditions in which one lives (Elliott et al., 2007; Felce & Perry, 1995). It may also be defined as the difference between a person's expectations and their present experiences (Aberg et al., 2005). A number of factors can influence quality of life, including mental health, physical ability, social function, and independence (Carr et al., 2001). Indeed the components that make up a good quality of life will be unique for each individual, yet, vision is consistently a key determinant (Altangerel et al., 2004; Cahill et al., 2005). The concept of vision-related quality of life can be described as the extent to which an individual is satisfied with their visual ability and how their vision impacts their day-to-day life (Asaoka et al., 2011).

1.6.1 Assessment of vision-related quality of life

Vision-related quality of life can be assessed using qualitative or quantitative methods. In clinical practice, vision-related quality of life is often assessed qualitatively whereby the patient is asked about their visual function, general wellbeing, and satisfaction with their care. This form of history taking is typically performed when the patient attends clinic appointments. Based on the patient's responses, an assessment will be made whether to continue or adjust the patients' treatment plan. When vision-related quality of life is measured in clinical studies, research protocols usually favour quantitative assessments, such as standardised, self-reported questionnaires, typically referred to as

patient-reported outcome measures (PROMs). Unlike qualitative history taking, PROMs provide a more robust method to quantify vision-related quality of life.

1.6.2 Patient reported outcome measures (PROMs)

The use of PROMs in research is well established and can provide valuable evidence regarding patients' quality of life and can contribute to the patient care journey in a number of ways, including: improving communication between the physician and patient; identifying and prioritizing problems for treatment; screening for unmet needs that warrant referral; identifying patient preferences among outcome goals with anticipated benefits to adherence to treatment; monitoring changes that may not be evident via clinical testing; training new staff in clinical skills; and informing clinical audit and clinical governance (Higginson & Carr, 2003). Much of the usage of PROMs has been within observational studies and clinical trials in a number of fields of medicine, including cardiology (Cleland et al., 2009), oncology (Luckett et al., 2009), and osteology (Hamilton et al., 2013). Attention is now being placed on involving the patient throughout clinical innovation, and PROM data are increasingly being used to provide evidence for drug and device approval (Food and Drug Administration, 2006). Furthermore, there is growing attention directed towards the optimisation and personalisation of PROMs through the use of item banking and computerised adaptive testing techniques. Qualitative research in the area of diabetic eye disease has been used to develop a diabetic retinopathy-specific quality of life item bank (Fenwick et al., 2010). An item bank is a set of items used to measure a specific domain that have been calibrated for difficulty on the same scale. Items are selected from the item bank by a computer algorithm according to the perceived ability level of each participant and their responses to previous questions until a predefined stopping criterion (e.g. measurement precision or number of items) is reached (Lamoureux & Fenwick, 2019). Lamoureux et al. (2019) describes this method as, if a patient has no difficulty with 'cooking a meal', the next selected item would relate to a task which is assumed to be a more difficult task such as 'reading the newspaper'. Conversely, if 'negotiating stairs' is a challenge, a presumed 'easier' task like 'watching TV' will be presented. Item banking and adaptive testing may provide a more sophisticated and user-friendly approach to assessment of patient-reported outcomes than traditional paper-pencil PROMs as they may be flexible and adaptable, potentially allowing for more precise and valid measurements of the desired domain, with the added benefit of fewer items required for the patient to complete (Gershon, 2005). Yet, it can

be argued that the assumption in computer adaptive testing that certain tasks are presumed to be easier and therefore not relevant to be questioned is directly in contrast of the 'user-friendly' and patient-centred approach that the model seeks to achieve. Indeed, the use of computer adaptive testing method in quality of life assessment in ophthalmology remains in its infancy, and a tool specifically designed to assess glaucoma remains under construction (Lamoureux, 2018).

PROMs can be useful to systematically measure changes in visual functional ability over time, as well as monitoring changes in patient satisfaction. Patient-reported outcome measures can be broad, assessing multiple aspects of general health and quality of life, or highly focused on a particular attribute. Most PROMs are based on self-evaluation of function and feature several items relating to a specific functional ability. Typically, respondents will mark their answers on a Likert scale (e.g. scored 0 to 5). An example of a PROM structure and response scale is shown in Figure 1.6. PROMs can be broadly divided into those assessing general health, system specific, or disease specific, all of which have been used to assess quality of life in patients with glaucoma.

General health-Related PROMs: These measures are typically used to assess the effects of interventions and vision loss on quality of life. An important benefit of these instruments is they allow for an overview of health which can be compared to other diseases. An example of a general health-related PROM is The Medical Outcomes Study Short-Form Health Survey (SF-36) (Ware & Sherbourne, 1992) which measures patients' health perceptions in a number of areas – general health, physical function, role limitations due to physical and mental disability, social function, vitality, mental health, and bodily pain. The sensitivity of the SF-36 at detecting treatment effects and disease progression is assessed in a later chapter of this thesis.

Vision-specific PROMs: Initially, the primary goal of vision-related quality of life instruments was to assess the effect of cataract on patients' perceived visual function (Mangione et al., 1992). Vision-specific PROMs are now widely used in various aspects of ophthalmic research (Glen et al., 2011; Hamzah et al., 2011). These PROMs assess ocular symptoms and specific difficulties with tasks which rely on vision. Questions relating to a similar theme are often grouped into subscales. For example, questions such as *'Because of your eyesight, how much difficulty do you have seeing how people react to things you say?'* and *'Because of your eyesight, how much difficulty do you have visiting with people*

in their home, at parties, or in restaurants?' are often used to assess the subscale of Social Functioning. Vision-specific PROMs are likely to provide more clinically useful information about the impact of the disease on the patient, but do not allow for comparison with non-ocular disease states (Spratt et al., 2008). A commonly used vision-related quality of life instrument, the National Eye Institute visual functioning questionnaire (NEI VFQ-25), is used to assess the impact of visual functioning in Chapter 2 of this thesis.

Glaucoma-specific PROMs: These instruments were developed to better discriminate between patients with glaucoma from individuals with healthy vision. Glaucoma-specific PROMs are more likely to correlate with visual field loss in patients with glaucoma than instruments relating to general health (Spaeth et al., 2006). Questions typically relate to visual ability, task performance, and the impact of reduced visual ability on the patient. An example of a glaucoma-specific PROM, the Glaucoma Quality of Life (GQL-15) is shown in Figure 1.6. The GQL-15 has previously been found to demonstrate discernible differences between glaucoma patients with mild visual field loss compared to control individuals (Nelson et al., 2003). This finding challenges the belief that glaucoma is an asymptomatic disease in its early stages. The sensitivity of glaucoma-specific PROMs at detecting changes in disease-state is assessed in Chapter 3 of this thesis.

Indeed, asking a patient directly is an effective way to ascertain how they feel about their condition and how it might be affecting their well-being (Deshpande et al., 2011). However, a fundamental problem with PROMs is that they are subjective, and no single instrument covers all aspects of patients' vision-related quality of life (Somner et al., 2012). As such, using PROMs to assess how glaucomatous visual loss is affecting patients can be problematic, especially as the disease is often asymptomatic. However, PROMs are now being used as primary outcome measures in glaucoma clinical trials (Azuara-Blanco et al., 2016; King et al., 2017; Vickerstaff et al., 2015) and there is good rationale for using outcomes that are directly relevant and meaningful to the patient. Yet, it is possible that PROMs are not as sensitive to changes in visual function as clinical measures of functional loss, like automated perimetry. As such, it is proposed that the sensitivity of PROMs when used in glaucoma trials is examined and this is the focus of Chapter 3 in this thesis.

Does your vision give you any difficulty, even with glasses, with the following activities?						
	None	**A little bit**	**Some**	**Quite a lot**	**Severe**	**Do not perform**
Reading newspapers	1	2	3	4	5	0
Walking after dark	1	2	3	4	5	0
Seeing at night	1	2	3	4	5	0
Walking on uneven ground	1	2	3	4	5	0
Adjusting to bright lights	1	2	3	4	5	0
Adjusting to dim lights	1	2	3	4	5	0
Going from light to dark room or vice versa	1	2	3	4	5	0
Tripping over objects	1	2	3	4	5	0
Seeing objects coming from the side	1	2	3	4	5	0
Crossing the road	1	2	3	4	5	0
Walking on steps/stairs	1	2	3	4	5	0
Bumping into objects	1	2	3	4	5	0
Judging distances of foot to step/curb	1	2	3	4	5	0
Finding dropped objects	1	2	3	4	5	0
Recognising faces	1	2	3	4	5	0

Figure 1.6: An example of a patient-reported outcome measure where 15 items use a 6-point Likert scale for individual responses. This figure was reproduced from Nelson et al., (2003).

1.6.3 Vision-related quality of life in glaucoma

It is important to assess the impact of glaucoma on vision-related quality of life for all patients with the disease. Insight into how glaucoma affects vision-related quality of life might offer a means of developing treatment strategies tailored towards the individual's needs. It has been shown that good vision is valued much more highly than clinicians realise (Brown et al., 2006) and that ophthalmologists frequently underestimate the impact of glaucoma on the patient's life (Brown et al., 2000). An understanding of how glaucoma impacts on the lives of patients and their families can alert clinicians to potential strategies to help ease the burden of the disease. For example, knowledge that glaucoma patients may have greater difficulty under poor light conditions may prompt evaluation of the patient's home, whereby lifestyle suggestions can be made, such as ensuring suitable lighting or minimise obstacles (Livengood & Baker, 2015). Furthermore,

an understanding of vision-related quality of life in the later stages of the disease may help to educate other patients about the possible future impact of glaucoma on their lives (Newsham et al., 2007). In addition, knowledge of when daily tasks become affected by glaucomatous visual loss may have a key role in determining when to begin treating the patient, or making changes to current treatment plans. As the main aim when treating glaucoma is to maintain vision-related quality of life, having an understanding of how a decline in visual function can negatively impact the patient's life is imperative. Research into the association between glaucoma and vision-related quality of life is often disjointed and has produced conflicting results. For that reason, this thesis (Chapter 2) aims to further explore this relationship and provide new insights into the knowledge of vision-related quality of life and glaucoma.

1.7 Visual disability

Visual function can relate to many aspects of daily living where having good vision can determine how well a task can be completed. Studies have highlighted that pathologies which affect vision, such as glaucoma, can affect a broad array of activities (Gutierrez et al., 1997; Mills et al., 2001; Parrish et al., 1997; Ringsdorf et al., 2006). When assessing visual function in people with eye disease, it is important to consider how the disease impacts ability to complete activities that are most important to individuals, as well as activities that are most likely to be affected by the disease (Ramulu, 2009). Growing emphasis is now being placed on the self-reported visual function of individuals with glaucoma. This is, at least in part, due to recent guidelines set by the European Glaucoma Society (EGS) which states that maintaining patients' vision-related quality of life is paramount when treating glaucoma (EGS, 2017).

1.7.1 Visual disability in glaucoma

There is good clinical evidence to indicate that vision-related quality of life is impaired in patients with glaucoma (Janz et al., 2001; Spaeth et al., 2006). Deterioration in visual function has a major influence on vision-related quality of life related to glaucoma (Medeiros et al., 2015). Reductions in vision-related quality of life have been specifically attributed to the progressive loss of visual field (McKean-Cowdin et al., 2008; Hyman et al., 2005). Research has focused on establishing which specific tasks may be most affected in glaucoma (Glen et al., 2011). Many of these tasks would be routine activities for the patient, and so a decrease in ability, or a total inability, to perform these tasks can have

significant consequences for the patient's vision-related quality of life. It has previously been suggested that the impact of visual disability on vison-related quality of life is unlikely to be a linear relationship (Peters et al., 2015). This is because many daily tasks can still be performed in the early stage of glaucoma, however these tasks become more difficult to achieve as the disease advances. Rather, there is likely to be a visual disability 'threshold' where vision-related quality of life will decline more rapidly once routine tasks can no longer be performed. The concept of a visual disability threshold is further investigated in this thesis (see Chapter 2).

The following sections will consider some of the most common visual function-related difficulties experienced by patients with glaucoma.

1.7.2 Lighting conditions

Patients with glaucoma frequently report difficulty when adjusting to different light intensities or glare (Burr et al., 2007; Nelson et al., 1999). Specifically, having difficulty with glare and light adaptation have been ranked as the most problematic symptom of glaucoma; more so than trouble with mobility, reading, and socialising (Nelson et al., 1999). Case-control findings suggest glaucoma patients are more likely to report difficulty with glare and lighting adaption compared to healthy-sighted observers (Lee et al., 1998; Sherwood et al., 1998). Interview and questionnaire studies have highlighted that problems with glare and lighting are frequently reported in patients with even mild stage glaucoma (Burr et al., 2007). Glaucoma suspects with impaired scotopic vision are more likely to have signs of early optic nerve injury (Glovinsky et al., 1992), suggesting that difficulty with light adaption may be one of the earliest symptoms presented in patients with glaucoma. It is in the domain of lighting and glare that the greatest change in self-reported disability occurs as glaucoma worsens (Burr et al., 2007; Nelson et al., 1999). This would suggest that difficulty with lighting and glare becomes more profound in the moderate and advanced stages of the disease.

Few studies have specifically investigated the role of lighting conditions on task performance in glaucoma. In a review of glaucoma-related disability, Ramulu highlighted that the lighting conditions under which tasks are performed may be more important than the task itself (Ramulu, 2009). Yet, this aspect of glaucoma disability remains largely unexplored.

1.7.3 Reading

With the exception of such tactile writing systems as Braille, reading is an example of a routine activity that relies entirely on vision. Typically, reading refers to the ability to read text at close range, as with reading a book, and so requires good near vision. However, ability to read may not solely rely on near vision, but also reading at greater distances, such as with reading road signs, text on television, and bus numbers. When reporting on reading ability, studies tend to assess the ability to read at near distances. Difficulty with near vision is common among visually impaired patients (Burr et al., 2007), and problems with reading are frequently reported among patients with glaucoma (Mangione 1998; Freeman, 2008; Parrish et al, 1997; Sherwood et al., 1998). The magnitude of reading difficulty is a concern given the high level of importance patients with glaucoma give to this everyday task (Burr et al., 2007).

Reading ability is often determined based on the patient's own perception of their reading speed. Yet, self-reported reading speed and actual performance may not correlate (Friedman et al., 1999). Few studies have directly investigated the impact of glaucoma on actual reading ability. In patients with bilateral visual field loss, reading speed has been found to be reduced when completing both silent and out-loud reading tasks compared to controls (Ramulu et al., 2013; Burton et al., 2014). In addition, prolonged periods of reading can incur greater fatigue among glaucoma patients (Nguyen et al., 2014), possibly attributed to the increased saccadic frequency and a tendency to lose fixation (Burton et al., 2014).

1.7.4 Mobility, balance, and driving

Mobility is a key component to living an independent lifestyle and so, not surprisingly, patients with reduced vision place high value on having good mobility (Aspinall et al., 2008). There are a wide variety of daily tasks where mobility has an essential role, such as grocery shopping and moving up and down steps. Mobility is strongly correlated with glaucomatous visual field loss (Friedman et al., 2007; Viswanathan et al., 1999; Black et al., 2011) and patients with glaucoma are more likely to suffer injuries from falls compared to individuals with healthy vision (Haymes et al., 2007). Moreover, glaucoma patients usually have slowed walking speeds (Turano et al., 1999), which may in part be due to a higher level of concentration required to avoid hazards.

Studies indicate that glaucoma appears to be associated with impaired balance. It has been reported that patients with glaucoma have increased postural instability when performing objective assessments of balance (Black et al., 2008) and binocular mean deviation has been shown to be a significant predictor of balance ability (Kotecha et al., 2012). While visual inputs are an important attribute for a good sense of balance, there are a number of systems which contribute towards postural stability, where a complex interaction between the vestibular, somatosensory, and visual systems is required (Massion, 1994). Yet, when performing balance related assessments with eyes closed, glaucoma patients perform similarly to control patients (also with eyes closed) (Shabana et al., 2005), indicating that loss of vision is a key factor in worsening balance among glaucoma patients.

In addition to reduced walking speed and higher likelihood of falls, impaired mobility and balance can result in social isolation and be detrimental to overall general health. One study found that patients with glaucoma are more likely to avoid going outdoors, possibly due to fear of injury (Ramulu et al., 2012) and avoidance of outdoor activities was found to increase as glaucomatous visual field loss worsens. In addition, a reduction in physical activity has been linked with a host of chronic diseases including: diabetes, cancer, osteoporosis, and disorders affecting the cardiovascular system (Warburton et al., 2006).

The transportation of choice for many older adults is driving (Eberhand, 1998) and therefore is a key component of mobility. Diseases which impair functional ability, such as glaucoma, can make it difficult for patients to continue to be safely mobile. Loss of driving ability is one of the most feared aspects for patients diagnosed with glaucoma (Bhargava et al., 2006), and a significant proportion of people with glaucoma will be declared as unfit to drive (Ang & Eke, 2007). Loss of driving license can have a considerable impact on quality of life due to its ramifications on social independence and self-esteem. Indeed, elderly people who have stopped driving are at risk of worsening depressive symptoms (Fonda et al., 2001) and are more likely to stay indoors (Marottoli et al., 2000), or be moved into long-term care (Freeman et al., 2006). For patients still driving, glaucoma can pose significant problems, including more self-reported difficulty when driving (Freeman et al., 2008) and more likely to be involved in traffic accidents (Szlyk et al., 2005).

1.7.5 Visual search and face recognition

Visual search refers to the ability to pick out a specific object in a scene, such as locating an item on a supermarket shelf. Visual search is an example of a routinely performed task where visual ability plays a key role. Glaucoma patients report difficulties when searching for specific objects, especially in cluttered environments (Goldberg et al., 2009; Nelson et al., 2003). Objective assessment of visual search ability may offer a more clinically useful indication of visual disability among patients with glaucoma (Crabb & Taylor, 2017). Studies adopting a more objective assessment of visual search ability show that the time taken to complete real-world search tasks suggest that glaucoma patients have greater difficulty when searching for objects compared to age-matched controls (Smith et al., 2012; Smith et al., 2011).

Qualitative research has indicated that patients with glaucoma can struggle to identify faces, such as characters on television or friends and neighbours in the street (Glen & Crabb, 2015). There is evidence to suggest individuals with advanced glaucoma may have more difficulty with recognising faces than healthy-sighted peers (Glen et al., 2012). Problems with face recognition have been found to have long-term effects, whereby patients may begin to avoid social situations and can have difficulty in gaining employment (Yardley et al., 2008).

1.8 Patient journey in glaucoma

As discussed previously (see section 1.6.2), glaucoma can have a significant impact on patients' vision-related quality of life. Glaucoma will mainly affect quality of life through visual disability, whereby routine activities become progressively more difficult to complete and restrict individuals' ability to live an autonomous life. However, glaucoma can negatively influence quality of life in numerous ways, including the burden of ongoing therapy and hospital visits, unpleasant side effects of treatment, anxiety associated with living with a chronic disease, and fear of future visual loss (Janz et al., 2007; Wu et al., 2011).

The concept of the 'patient journey' for those living with chronic conditions has garnered increased attention in recent years. The British Medical Journal (BMJ) has published a number of commentary articles whereby patients have detailed their personal journey of living with chronic illnesses (Lapsley & Groves, 2004), including stories of Parkinson's disease, dementia, and also glaucoma (Baker & Graham, 2004;

Dartington, 2008; Hartmann & Rhee, 2006). The aim of these such articles is to describe the difficulties faced when diagnosed with a chronic condition and how this impacts on quality of life. Stories of the patient journey can be a rich source of knowledge which can facilitate an understanding between patients and healthcare professionals, beyond that offered by clinical examination or formal case history (Lapsley & Groves, 2004). As such, stories of the patient journey can advise others of what really matters to the patient, and what can be done to help. Hartmann and Rhee give an explicit insight into the subjective experience of the journey as a patient with glaucoma. Notably, the authors discuss the burden of frequent visits to eye clinics and the distress of non-effective medication and surgery.

Qualitative research has considered the impact of glaucoma to be on a spectrum, whereby the earliest stage, as well as the later more advanced stage of the disease, represent particularly challenging time points in the glaucoma patient journey (Cross et al., 2009). This concept of the glaucoma impact 'spectrum' makes clinical sense as, in the earliest stages, the patient must come to terms with living with a chronic disease, the burden of hospital visits and medications, and the fear of worsening functional ability. For late-stage disease, these patients have experienced unprecedented psychological challenges such as worsening vision and a decline in visual ability, and the ordeal of invasive and possibly fruitless surgical intervention. The aim of this thesis is to shed further light onto the patient journey in glaucoma and to understand the impact of the disease on patients' quality of life. Because it is rational to consider the impact of glaucoma on a spectrum, this thesis will pay particular attention to the stages of the disease which are likely to have the greatest impact on the patient – the early and late stages of glaucoma.

1.9 Rationale and aims of PhD

In order to better understand the impact of glaucoma, it is necessary to conduct evidence-based research to investigate how the disease affects the patient's daily life. Such research may help to promote awareness of the disease and can serve as an important resource for improving the patient journey in glaucoma. Aspects of the patient journey investigated in this thesis relate to a number of key issues in the field of glaucoma and ophthalmology. Specifically, the following aims were investigated:

1. To investigate the relationship between vision-related quality of life and clinically measured visual function. Vision-related quality of life is a pivotal component to good overall wellbeing. The hypothesis was that individuals with glaucoma will self-report different levels of vision-related quality of life depending on the severity of their disease. Results are discussed in the context of previous vision-related quality of life research in glaucoma (see Chapter 2).

2. To assess quality of life measures when used with patients recruited to The United Kingdom Glaucoma Treatment Study. Patient-reported outcomes play a significant role in clinical trials. This study examined glaucoma patients' responses on a number of frequently used PROMs and assessed whether such instruments are appropriate to be used as primary outcome measures in clinical trials. In addition to enhancing our understanding of the impact of glaucoma in the early stages of the disease, this study may have implications for the design of future clinical trials in glaucoma (see Chapter 3).

3. To examine a novel service for monitoring glaucoma patients in the hospital eye service. This study audited a virtual glaucoma monitoring service with the use of a 'big data' approach. Results are discussed in relation to how novel monitoring systems may help to reduce the burden glaucoma may have on patients and their caregivers and how this may have a subsequent impact on quality of life (see Chapter 4).

4. To understand the patient and surgeon perspectives of high-stakes surgical intervention in advanced glaucoma. For the study described in this chapter, individuals with experience of 'only-eye' surgery were interviewed about their thoughts of glaucoma surgery performed on individuals with only one functioning eye. Both patients and surgeons were asked to recall their experiences of these high-stakes procedures using semi-structured interviews. Interview transcripts were thematically analysed and generated a number of key themes relevant to only-eye surgery. The results of this study highlight the challenges to overcome when caring for patients with advanced glaucoma (see Chapter 5).

Chapter 6 gives a summary of the main findings from these research studies and are discussed in the context of the implications for individuals living with glaucoma and potential areas for future work.

Chapter Two - The relationship between loss of visual field and vision-related quality of life

Glaucoma will impact the daily life of a patient with the disease. If a person's glaucoma is not clinically stable, the disease can progress and can cause increased visual disability (Ramulu, 2009). However, visual disability is not the only reason for decreases in glaucoma patients' wellbeing and vision-related quality of life. Rather, causes for decline in vision-related quality of life are multifactorial and include the burden of ongoing therapy, unpleasant side effects of medication, stress of ongoing treatment, fear of further visual loss, strain on informal care givers, and burden of repeated clinic visits for disease monitoring. As expected, the psychological burden of glaucoma increases as vision decreases, along with a growing fear of blindness and visual disability (Janz et al., 2007), and an increase in depressive symptoms (Wang et al., 2012). The purpose of this chapter was to analyse the impact of glaucoma on vision-related quality of life among patients with a range of disease severity. The aim was to achieve a greater understanding of the patient journey in glaucoma by highlighting stages where glaucoma might have the greatest impact on the patient.

The work presented in this chapter has formed a paper published in *Journal of Ophthalmology* (Jones et al., 2017); see list of supporting publications. The co-authors of this work are David Crabb (DC) and Susan Bryan (SB). Help with the spline-fitting method of data analysis, data visualisation, and calculation of the Akaike Information Criterion (AIC) came from SB and DC. Data were collected by Prior et al., 2013 as part of the pilot Aberdeen Glaucoma Questionnaire (AGQ) study. Access to the data was approved by Jennifer Burr (JB). The AGC study is a component of a Medical Research Council funded strategic grant, G0701759: Developing the intervention and outcome components of a proposed randomised controlled trial of a national screening programme for open angle glaucoma. Data analysis was performed by Lee Jones (LJ). The paper was written by LJ, and reviewed, edited, and approved by SB and DC.

2.1 Introduction

The loss of visual field sensitivity is hallmark in patients with glaucoma (Crabb, 2016). This loss in sensitivity can pose as a significant threat to patients' everyday functioning and quality of life. It is often the case that glaucoma patients report greater difficulty in performing vision-related tasks as the severity of the disease increases and the damage to the visual field worsens (Ramulu, 2009; Jampel et al., 2002; van Gestel et al., 2010; Gutierrez et al., 1997; Parrish et al., 1997; McKean-Cowdin et al., 2007). However, it is not uncommon for the effects of glaucoma to go undetected by the patient (Crabb, 2016; Quigley & Broman, 2006). For example, many performance-based studies demonstrate that glaucoma patients can perform within the normal expected range, even in cases of advanced visual field loss (Burton et al., 2014; Smith et al., 2012; Smith et al., 2011; Kotecha et al., 2009; Glen et al., 2012). Conversely, there is evidence to suggest that even mild or moderate glaucomatous disease may have an impact on the patient's quality of life (Alqudah et al., 2016).

Assessment of vision-related quality of life typically involves self-reported response to questionnaires. These questionnaires, also referred to as 'instruments', feature items whereby patients mainly document the extent to which they struggle to complete routine tasks. The NEI VFQ-25 (Mangione et al., 2001) has been widely used in ophthalmology research as a measure of vision-related quality of life. This instrument was used in a landmark report revealing the association between visual field loss and health-related quality of life in glaucoma (McKean-Cowdin et al., 2007), and has been widely used in other cross-sectional studies (Jampel et al., 2002; van Gestel et al., 2010; Gutierrez et al., 1997; Parrish et al., 1997; Alqudah et al., 2016; Mills et al., 2001; Sumi et al., 2003). However, these studies report only a modest relationship between vision-related quality of life and visual field damage. More recently, longitudinal studies of glaucoma patient cohorts have highlighted NEI VFQ-25 scores to be impacted by location and speed of visual field loss. (Abe et al., 2016; Medeiros et al., 2015; Gracitelli et al., 2015).

Association between visual field loss and worsening of vision-related quality of life reported in the literature mainly implies that the relationship is a linear one (McKean-Cowdin et al., 2007; Alqudah et al., 2016; Abe et al., 2016; Medeiros et al., 2015). That is, vision-related quality of life constantly declines as the visual field worsens. In fact, the

relationship between loss of vision-related quality of life and visual field worsening is likely better described as a monotonic one. In other words, whilst vision-related quality of life never improves as the visual field worsens, the decline could have slow or rapid stages, or even remain relatively constant for a phase. This idea, relatively unexplored, is the subject of this study.

Patients with glaucoma are typically asymptomatic in the early stages of the disease process. Any change in visual field status may be compensated for by good binocular vision or is simply not noticed. As visual field loss becomes symptomatic a patient is more likely to self-report an impact on vision-related quality of life, but in turn patients may adapt to their vision loss. Indeed, there is some evidence that behavioural adaptions, such as adjusted head and eye movements, can help glaucoma patients compensate for their vision loss when completing everyday tasks (Burton et al., 2014; Smith et al., 2012a; Glen et al., 2013; Smith et al., 2012b; Crabb et al., 2014; Glen & Crabb, 2015; Hassan et al., 2015). Eventually as glaucoma worsens, visual field loss will likely impact on legality of driving and restrict mobility and confidence (Glen & Crabb, 2015; Hassan et al., 2015; Friedman et al., 2007; Kotecha et al., 2012; Black et al., 2011; Yuki et al., 2013; Ramulu et al., 2012; Ramulu et al., 2014).

Patients with more advanced glaucoma report significantly worse scores on the NEI VFQ-25 compared to their better sighted peers. In a cross sectional analysis of an established cohort of 233 patients from the Early Manifest Glaucoma Trial (EMGT) (Heijl et al., 2002), Peters and colleagues hinted at the idea of accelerated worsening of vision-related quality of life once patients reach a certain visual field threshold (MD of -18dB or worse) in their least affected or 'better' eye (Peters et al., 2015). This evidence suggests a 'tipping point' after which each decibel of visual field loss will have more severe consequences for patients' vision-related quality of life. This observation is worth further study. Thus, the purpose of this study was to investigate the relationship between vision-related quality of life (using NEI VFQ-25 scores) and a summary measure of visual field loss (the MD) amongst a spectrum of disease severity in a large number of patients from a glaucoma clinic. Specifically, we consider that the rate of decline in vision-related quality of life may not simply be a linear process and we look for statistical evidence of different phases of decline or periods where there might be more or less rapid reduction as the visual field worsens.

2.2 Methods

This study took advantage of anonymised patient data collected as part of an investigation of conducting a randomized controlled trial for glaucoma screening in the United Kingdom (UK) (Burr et al., 2014). The data, collected from a cross-sectional postal survey, is described in detail elsewhere (Prior et al., 2013) but is also summarised below.

Potential participants were identified by an ophthalmologist from an electronic patient record (Medisoft, Leeds, UK) of visual fields at a hospital based glaucoma service in London (Moorfields Eye Hospital NHS Foundation Trust). Recruitment criteria required potential patients to have at least two entries in the database having undergone visual field testing on a Humphrey Visual Field Analyser (HFA; Carl Zeiss Meditec, CA, USA) between January 2007 and September 2009. To be included, patients were required to have reproducible HFA 24-2 (SITA Standard) visual field defects in both eyes at the two most recent visits as determined by the Glaucoma Hemifield Test (GHT) (Åsman & Heijl, 1992). The GHT results had to be "borderline" or "outside normal limits" as recorded in the electronic patient record on both occasions. A total of 1349 patients were considered as suitable for study recruitment. Ethical approval was granted and the study adhered to the Declaration of Helsinki.

Questionnaires were posted to all patients considered suitable for the study in March 2010. Included with the questionnaire was a participant information sheet, a letter of invitation from their consultant ophthalmologist, and a reply paid envelope. The postal questionnaire comprised of four elements: a pilot instrument of the Aberdeen Glaucoma Questionnaire; a measure of overall general health (EQ-5D); questions relating to baseline demographics; and the vision-specific PROM, the NEI VFQ-25 (Mangione et al., 2001). This instrument consists of 25 items across 12 subscales, where 11 constructs are vision-related (General Vision, Ocular Pain, Near Activities, Distant Activities, Social Functioning, Role Difficulties, Mental Health, Dependency, Driving, Colour Vision, and Peripheral Vision) and one construct regarding general health. A reminder letter was sent two weeks after initial contact. No further contact was made with those who did not return the questionnaire. The return of completed questionnaires was considered as consent to take part in the study. A total of 656 questionnaires were returned. Ethics committee approval was obtained for the study from the North of Scotland Research Ethics Committee (Ref: 09/S0802/107). For those returning the questionnaire, we

obtained data from the visual field databases on visual field parameters, mean defect and pattern standard deviation.

The HFA MD in the least affected eye (Best eye MD; BEMD) recorded at the most recent clinical visit to when the questionnaire was administered was used as the surrogate measure of visual field loss. The MD is conventionally used in the clinic and in clinical trials; it is a summary measure of the overall reduction in visual field sensitivity relative to a group of healthy age-matched observers, with more negative values indicating more vision loss. We used the BEMD since this best reflects the patients' visual field morbidity (Arora et al., 2013). Numeric responses on the NEI VFQ-25 were re-coded in line with the scoring guidelines (Mangione et al., 2001). Each item is converted into a value ranging from 0 to 100 where higher scores indicate greater vision-related quality of life and lower scores indicative of poorer vision-related quality of life. A composite score for vision-related quality of life was then calculated by averaging all vision-related subscales. In cases where more than 5% of the questionnaire data were missing, or where subscale scores were unable to be calculated due to insufficient data, responses were excluded from our analysis. In line with scoring guidelines, patients who had never driven a car had responses coded as 'missing' for the driving subscale (Mangione et al., 2001).

A total of 636 patients with complete NEI VFQ-25 and BEMD data were used for this analysis. No other data, apart from age (years) at the time of the most recent visual field, was considered.

We explored the relationship between BEMD and NEI VFQ-25 using the freeknotspline package in the statistical programming language R (www.R-project.org). This package fits free-knot splines to data with one independent variable and one dependent variable (Spiriti et al., 2013; Montoya et al., 2014). This technique will automatically highlight phases where a monotonic relationship between two variables may change. The points where the phases (segments) connect are called the knots of the spline. Knots can be determined a priori or by allowing the data to dictate areas where change occurs. A knot-search algorithm is provided for the case where the number of knots is not known in advance, as with these data. In the subsequent analysis it is then possible to compare the spline model that describes this relationship against a linear relationship (using ordinary least squares regression [OLSR]) by considering the Akaike information criterion (AIC); this is a measure of the relative quality of statistical models

for a given set of data, and provides a means for model selection (Akaike, 1976). Phases in the relationship between BEMD and NEI VFQ-25 identified by this approach were then further analysed using linear OLSR where a series of separate OLSR lines are fitted to appropriate ranges of BEMD. These analyses, including plotting the data, were performed in R (www.R-project.org) and SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

2.3 Results

Median (interquartile range; IQR) age of the 636 patients analysed was 70 (60, 77) years. Median (IQR) BEMD was -2.1 (-5.2, -0.4) dB and worst eye MD was -5.5 (-11.3, -2.3) dB. Median (IQR) composite score on the NEI VFQ-25 was 89 (74, 95) points. The majority of patients (97%) scored their general health to be good or better on the general health item of the NEI VFQ-25.

Figure 2.1 shows the distribution of patients' BEMD score against composite scores from the NEI VFQ-25. The red line (left-hand side plot) gives the best-fitting linear OLSR line (red line). This model assumes a linear association between BEMD and NEI VFQ-25. The blue line (right-hand side plot) shows the automatically chosen penalised spline model which had two knots with a polynomial of degree 3.

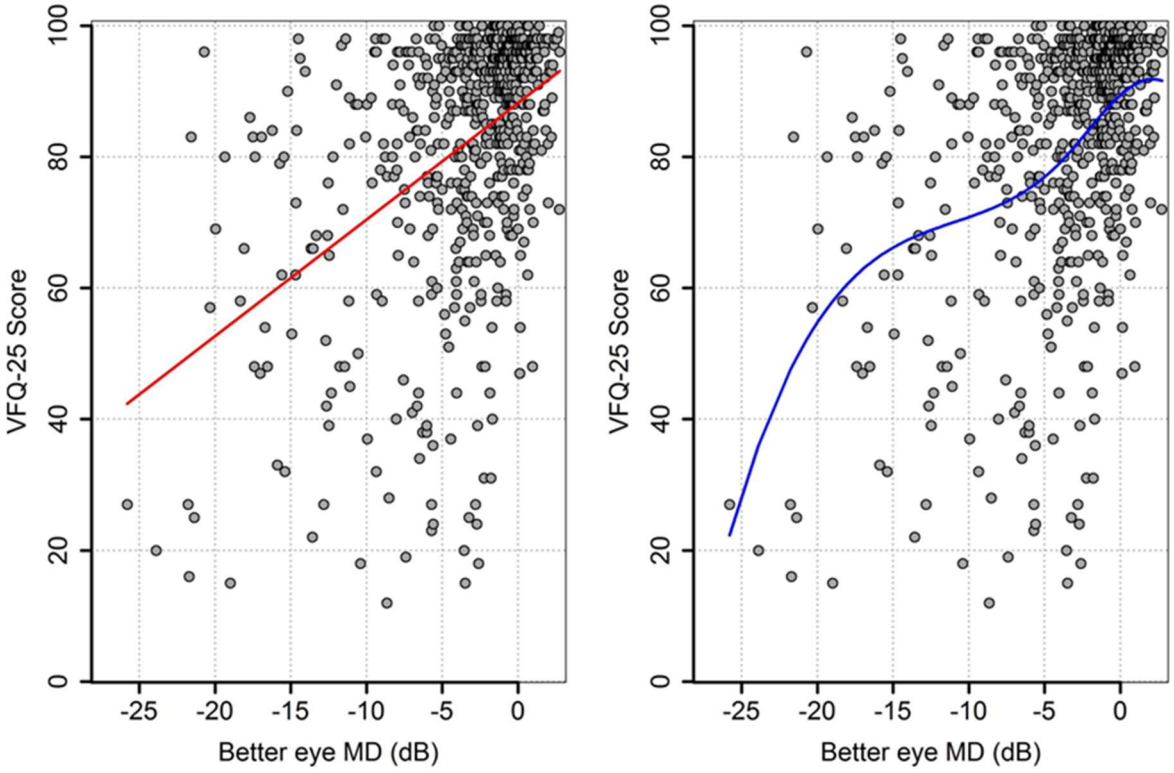

Figure 2.1: Points represent scores on NEI VFQ-25 compared to BEMD (dB) for 636 patients. The use of linear (red line) and spline (blue line) regression modelling assessing trend in relationship between the two variables.

The AIC index for the linear and spline models was 3601.7 and 3596.0 respectively. In simple terms the AIC index indicates stronger evidence for a preference of one model over another (the lower the better). There is some debate in the applied statistics literature about the meaning of small differences in AIC, but differences >5 (as with these data) indicate that the model with the lower AIC is likely to be more informative (Symonds & Moussalli, 2011). For the purposes of this study, this statistical interrogation of the relationship mainly suggests defined phases where NEI VFQ-25 deteriorates with more or less acceleration as a patient's BEMD worsens. On inspection there seems to be three phases in the association. For BEMD up to about -5dB there is a distinct slope followed by a phase (between -5 dB and -15dB) where the line flattens before it becomes much steeper again (worse than -15dB). Three OLSR lines were fitted to these three phases and the results along with 95% confidence limits are shown in Figure 2.2 with model parameters given in Table 2.1. Simply put, the average patient loses about 2 units (out of 100) on NEI VFQ-25 for every loss of 1 dB (BEMD) as their glaucomatous visual field loss become bilateral, up to -5dB. Worsening on NEI VFQ-25 then appears to slow down: the average patient loses about 1 unit (out of 100) on NEI VFQ-25 for every loss of 1 dB (BEMD) from -5 to -15dB. Finally, a more rapid phase of deterioration in vision-related quality of life seems to occur: after the BEMD worsens to around -15dB the average patient starts to lose 4 to 5 units on NEI VFQ-25 for every remaining loss of 1 dB (BEMD).

BEMD (dB)	**N**	**Slope (95% Confidence interval)**	**Standard error**	**p-value**
+2 to -5 (Yellow)	475	2.3 (1.5,3.0)	0.40	<0.001
-5 to -15 (Green)	132	1.1 (-0.3,2.5)	0.70	0.14
< -15 (Red)	29	4.6 (1.2, 8.0)	1.64	0.009

Table 2.1: Relationship between decline in NEI VFQ-25 score for piecewise regression analysis for each 1dB decline in BEMD score.

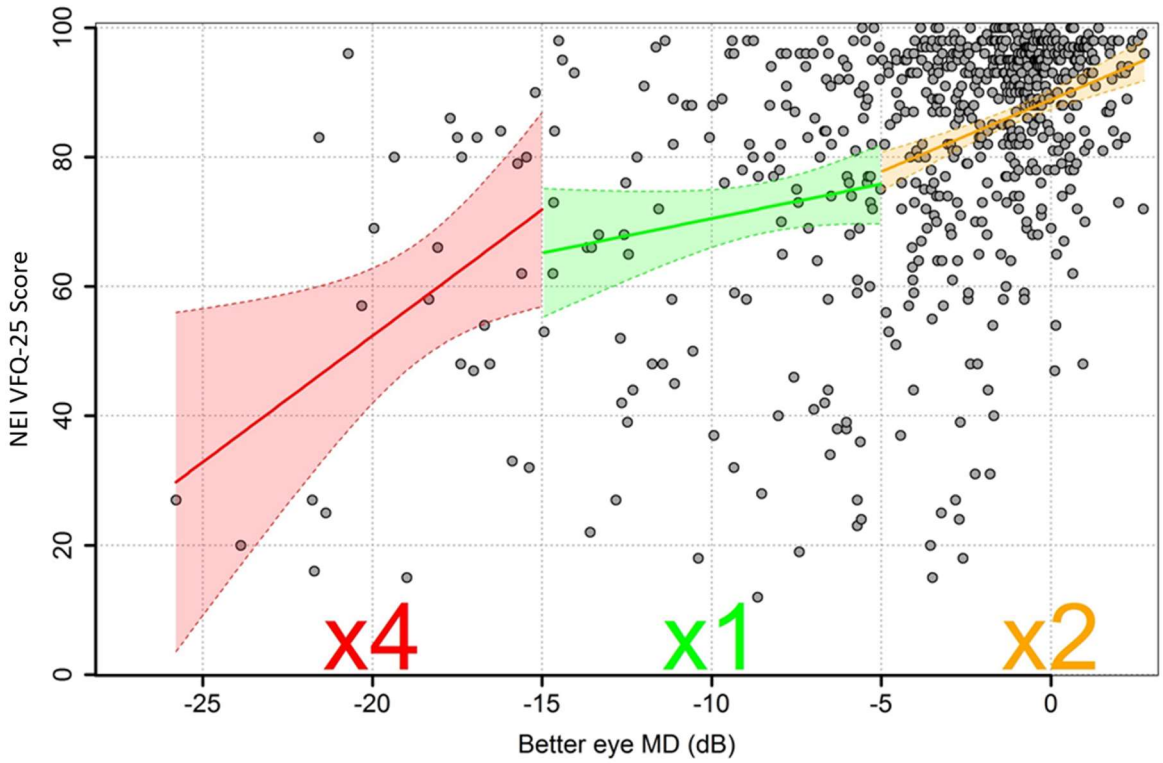

Figure 2.2: Fitting of three OLSR lines with 95% confidence limits for each phase of decline in vision-related quality of life. Points represent scores on the NEI VFQ-25 and BEMD in 636 patients. The green phase shows the slowest decline in NEI VFQ-25 score, the yellow line shows quicker decline where NEI VFQ-25 scores reduce 2 times faster than in the green phase. The red line shows decline on NEI VFQ-25 as about four times quicker than in the green phase.

2.4 Discussion

Economists anecdotally refer to bankruptcy happening in two stages – gradually then suddenly (Taylor, 2015). Hence, a monotonic process but not necessarily a linear one. In this study we provide some evidence that this is what happens in patients' perception of their vision-related quality of life as their glaucomatous visual field worsens in their better eye over time. Rather than a linear decline we suggest there are phases of change attributed to progression in the visual field in the least affected eye. The phases illustrated in the statistical associations we report make clinical sense. As the better-seeing eye gets measurable visual field loss (bilateral disease) the previously asymptomatic patient may begin to notice the impact of scotoma as they perform visual tasks. A phase of adaptation to this loss then might likely precede another phase where advanced loss in both eyes really impacts on vision-related quality of life. Our evidence isn't strong; it is merely based on a cross-sectional survey of people from glaucoma clinics with no supplementary clinical information. Yet our results support a concept that ought to be tested with other datasets or longitudinal studies. Better knowledge on how visual function decline may accelerate at different stages of the disease process would be useful for the clinical management of patients and also for health economists as they determine better utilities for evaluating glaucoma treatments.

Our findings add to current understanding of how patients perceive their difficulty living with glaucoma. Vision-related quality of life deteriorates as glaucoma worsens and our data supports this. This association is not particularly a strong one. For example, the R-squared (%) for the linear association between vision-related quality of life and BEMD data is 21% suggesting that only part of the variance in vision-related quality of life is explained by the visual field. Moreover, it is quite remarkable how some patients with BEMD worse than -20dB (top left hand corner of graph depicted in Figure 2.2) report vision-related quality of life to be the same or better than many patients with a BEMD of 0 dB or higher. This observation coincides with the findings of others indicating only a modest relationship between NEI VFQ-25 scores and visual field status (Jampel et al., 2002; van Gestel et al., 2010; Gutierrez et al., 1997; Parrish et al., 1997; Alqudah et al., 2016; Mills et al., 2001; Sumi et al., 2003). Our statistical treatment of our large cross-sectional data implies that this weak association may behave differently at different stages of BEMD severity and this is new knowledge. Our findings give some weight to the idea that the speed at which vision-related quality of life declines may alter

during different phases of the disease and that specific markers for BEMD could indicate change points in patient-reported functional ability.

Our observations of different phases of association between vision-related quality of life and BEMD are supported by the results from a twenty year follow up of patients in the EMGT (Peters et al., 2015). In a cross sectional analysis of this cohort of 233 patients, Peters et al. found a significant difference in Rasch-calibrated scores on the NEI VFQ-25 for patients with BEMD worse than -18 dB and those with BEMD better than -18 dB. In cases where BEMD was worse than -18 dB, patients' scores on the NEI VFQ-25 did not exceed 70 out of 100. This suggests different phases in the relationship between BEMD and NEI VFQ-25, with a threshold where impact of visual field loss accelerates. A strength of this study is that a wide range of glaucoma severity was analysed, whereas other studies consider only patients with early glaucomatous damage (Jampel et al., 2002; Alqudah et al., 2016).

In addition to supporting the concept of a non-linear relationship between vision-related quality of life and BEMD, our results also support recent findings regarding the impact of glaucoma on vision-related quality of life in the earlier stages of the disease. Our results indicate that a 1 dB decline in BEMD is associated with an average reduction of 2.3 units on the NEI VFQ-25 for patients with BEMD between +2 dB and -5 dB. This finding is similar to that of a longitudinal study by Alqudah et al. (2016) who found an association between scores on the NEI VFQ-25 and BEMD in the early stages of glaucoma. Their study was restricted to patients with BEMD between approximately +2.5 dB and -5 dB and they reported a decline of 0.5 units on the NEI VFQ-25 for each 1 dB reduction.

Our findings become important when considering treatment options for patients with advanced stage glaucoma. It is evident that patients' vision-related quality of life reduces rapidly once BEMD loss becomes advanced. Decline in vision-related quality of life is approximately four times faster than in previous stages of the disease after patients' vision deteriorates beyond -15dB. This threshold may have important clinical implications when treating patients in the advanced stages of the disease. Due to the potential for fast decline in vision-related quality of life, this point could be used to guide potential intervention options when treating patients with advanced glaucoma. The suggestion has been made that more research is needed in order to determine the best treatment

option for advanced glaucoma (King et al., 2011), and this is currently under investigation in a randomised clinical trial (King et al., 2017). Our results may also have implications for those developing utilities for health economic models for glaucoma treatments (Boodhna & Crabb, 2016).

There are some strengths to our study. The sample size was large and we took advantage of a large database of recorded visual field data. These data represent unselected people in glaucoma clinics that are receiving routine care and therefore estimates are directly meaningful to 'real-world' practice. In addition, the patients in this study had a wide range of glaucoma severity. However, the proportion of patients with early visual field damage was greater than advanced cases and this could be perceived as a limitation.

Our investigation also had some limitations. The data used is cross-sectional and so we only consider patients' vision-related quality of life and visual field loss at a single time point. Moreover, measures of vision-related quality of life are self-reported. We are, for example, unable to account for the rate at which patients' visual field defect has progressed - and this has been shown to influence vision-related quality of life (Medeiros et al., 2015; Lisboa et al., 2013; Heijl et al., 2013). A better study design would use longitudinal data (Abe et al., 2016; Medeiros et al., 2015). Additionally, our study has the potential for response bias (49% response rate). However, given the adoption of a postal survey design and adherence to an ethical study protocol, a full response rate would be unlikely. As visual field data were unavailable for those who did not choose to participate, we were not able to consider the characteristics of non-responders. Nevertheless 49% is higher than response rates observed in studies using a similar design (Herndon et al., 2006). We did not have information on race, educational level, and marital status and these factors can influence quality of life. In addition, there may have been a large gap in time between patient's latest visual field data and when the completed NEI VFQ-25 was returned. The main problem with the design of this study is absence of any clinical indictors on the eyes other than the visual fields. We did not, for example, have information on co-existing cataract or detailed treatment history. Additionally, for this unselected sample, we did not have measures of visual acuity. A further disadvantage of our analysis is that we did not use a Rasch model to analyse the results of the NEI VFQ-25, whereas studies similar to ours have done this (Abe et al., 2016; Medeiros et al., 2015; Peters et al., 2015).

Our study opens up avenues for future research into the association between vision-related quality of life and clinical measures of vison loss. We found that the rate of decline in glaucoma patients' vision-related quality of life begins to slow after BEMD is reduced to -5 dB. This slow decline in NEI VFQ-25 scores remains evident until BEMD is reduced to -15 dB, where rapid decline occurs. More research is needed in order to understand what factors can influence the rate at which patient vision-related quality of life declines. A well designed prospective study should consider vision-related quality of life in people at this moderate or middle stage of disease and consider how they might be adapting to their visual field loss. Moreover, we used only one measure of vision-related quality of life, namely the NEI VFQ-25. Previous research has indicated that no single instrument covers all aspects of patients' vision-related quality of life (Somner et al., 2012). As such, replication of this study assessing responses on an instrument specific to glaucoma would be an interesting addition to the literature.

In conclusion, the relationship between vision-related quality of life and BEMD is a weak monotonic one. However, we provide some evidence to suggest this relationship may not be a linear one. The speed at which vision-related quality of life declines might better be described as gradually, where patients experience a period of adaption to their vision loss, and then suddenly, once patients' functional abilities become significantly impaired.

Chapter Three - Measuring changes in vision-related quality of life in glaucoma

It is important to measure the impact of a condition or therapeutic intervention on patients' lives. In clinical studies, the measurement and assessment of vision-related quality of life is often performed through the use of PROMs. As described in section 1.6.1, PROMs allow for patients to report their health perceptions, and any changes in these perceptions can be monitored by healthcare professionals and data analysts. PROMs also offer a more robust means of collecting quality of life data than methods such as qualitative history taking as PROMs can be systematic and easily repeated. The use of patient-centred outcomes is not only important for research, but it can also improve clinical practice (Basch et al., 2016; Chen et al., 2013). Well-crafted PROMs can realign clinicians' focus to something similar to the patient's needs and wants, and offer the promise of better and more meaningful clinician-patient relationships (Nelson et al., 2015).

In order to fully understand the impact of glaucoma on the patient's life, PROMs must be able to measure the multidimensional aspects of the disease including everyday visual challenges, discomfort of treatment, inconvenience of ongoing care, and psychological elements. The purpose of this chapter was to analyse glaucoma patients' responses on a number of frequently used PROMs and to assess whether these measures are sensitive to changes in glaucomatous disease severity. The aim was to enhance our understanding of the impact of glaucoma in the early stages of the disease, which may in turn have implications for the design of clinical glaucoma trials in the future.

The work presented in this chapter has been published in *Ophthalmology*, see list of supporting publications. The co-authors of this work are David Crabb (DC), David Garway-Heath (DGH), and Augusto Azuara-Blanco (AAB). Data were collected as part of the United Kingdom Glaucoma Treatment Study, a multi-centre, randomised, placebo-controlled clinical trial. Access to the data were granted by DC and DGH. Data analysis was performed by LJ. The paper was written by LJ, and reviewed, edited, and approved by all authors. The work presented in this chapter has also been presented as a paper presentation at the Association for Research in Vision and Ophthalmology meeting (Seattle, WA, USA, 2016) and The United Kingdom and Éire Glaucoma Society annual meeting (Cheltenham, UK, 2016); see list of supporting publications.

3.1 Introduction

Intraocular pressure (IOP) is currently the only modifiable risk factor for disease progression in glaucoma. All therapies approved for the treatment of glaucoma are licenced on their ability to reduce patients' IOP. Yet, the foremost outcome when treating glaucoma is to maintain what is most important to the patient, vision-related quality of life (European Glaucoma Society, 2017). Randomised clinical trials have provided evidence for the visual field preserving benefit of reducing IOP (Holmin et al., 1988; AGIS Investigators, 2000; Kass et al.,2002; Heijl et al., 2002; Pajic et al., 2010; Krupin et al., 2011; Anderson et al., 1998; Migdal et al., 1994; Jay & Murray, 1988; Musch et al., 2009; Garway-Heath et al., 2015). Recently, the United Kingdom Glaucoma Treatment Study (UKGTS) evidenced the effectiveness of an IOP lowering treatment in patients with glaucoma using visual field deterioration determined by standard automated perimetry as the primary outcome measure over a two-year follow-up period (Garway-Heath et al., 2015).

Typically, outcome measures in clinical trials are selected on their sensitivity to clinically meaningful changes in disease severity. However, diagnostic test measurements taken in the clinic do not directly capture the impact of glaucoma on the patient's life (Denniston et al., 2014). IOP is not a direct measure of glaucomatous optic neuropathy. Visual fields, however, indicate functional ability, and are therefore more closely associated with vision-related quality of life than IOP. PROMs are instruments derived from standardised, validated questionnaires that are used to measure perceived health status, functional status, or health-related quality of life. Asking a patient directly is an effective way to ascertain how someone feels about their condition and how it might be affecting their well-being (Deshpande et al., 2011). PROMs can also be readily translated into measures of cost-effectiveness.

Use of PROMs in clinical research has increased in recent years (Black, 2013), and this is beginning to be mirrored in glaucoma research (Glen et al., 2011), where a catalogue of vision-specific PROMs are now available (Hamzah et al., 2011). PROMs are also becoming more frequently used in clinical trials (Vodicka et al., 2015), including in ophthalmology trials, (Chakravarthy et al., 2013; Varma et al., 2012; Mitchell et al., 2011; Sugar et al., 2014; Lois et al., 2011). Typically, PROMs are used to complement a more clinical primary outcome in trials. However, The United States Food and Drug Administration endorses the use of PROMs as primary endpoints in glaucoma trials (Food and Drug Administration, 2006), and this has been implemented in recent glaucoma trials (Azuara-Blanco et al., 2016; King et al., 2018; Vickerstaff et al., 2015). An important

attribute of a clinical trial outcome measure is to be sensitive enough to detect differences between a treatment and a control group. This is particularly true for glaucoma treatment trials because the disease process is slow and changes to vision can be challenging to measure. Moreover, disease progression in glaucoma is often unnoticeable to the patient in the early stages of disease (Crabb, 2016). A lack of sensitivity may necessitate prolonged trial duration which can add to the delay of drug development. For this reason, the sensitivity of PROMs when used as outcome measures in glaucoma trials should be scrutinised and this is the subject of our study. Specifically, we analyse PROM responses from patients in the UKGTS to test the hypothesis that these measures can determine differences between the groups randomised to treatment or placebo.

3.2 Methods

In this study, we analyse the responses on PROMs of patients enrolled into the UKGTS, a multi-centre, randomised, triple-masked, placebo-controlled trial assessing visual function preservation in newly diagnosed open-angle glaucoma patients (trial registration number: ISRCTN96423140). Patients recruited from ten eye clinics throughout the United Kingdom were randomly allocated to receive an IOP reducing prostaglandin analogue Latanoprost (0.005%) or placebo eye drops. The UKGTS, and the subsequent analysis of anonymised data in this study, adhered to the tenets of the Declaration of Helsinki and was approved by local institutional review boards (ethics approval reference: 09/H0721/56). Study participants provided written informed consent.

A total of 461 patients from 516 enrolled were analysed in the trial (Latanoprost N = 231, placebo N = 230). Patients in the UKGTS were scheduled to perform a series of 11 visual field examinations during a 2-year observation period. Visual field progression was used as the primary endpoint in the trial. Progression analysis was performed in the Humphrey Field Analyser Guided Progression Analysis (GPA) software; a sensitive technique that considers changes at individual points (test locations) in the visual field. Progression was defined as at least three visual field locations worse than baseline at the 5% levels in two consecutive reliable visual fields and at least three visual field locations worse than baseline at the 5% levels in the two subsequent consecutive reliable visual fields; the locations identified in the first and second pair were not required to be identical.

Eligibility criteria for the UKGTS included presence of open angle glaucoma, defined as glaucomatous visual field defects in at least 1 eye with corresponding damage to the optic nerve head (cup-to-disc ratio of $\geq$0.7, focal narrowing of the neural rim, or both), with the presence of an open angle as determined by gonioscopy and the absence of retinal or neurological condition which may account for VF loss. The specific inclusion criteria for the study was as follows: newly detected, previously untreated open-angle glaucoma (including primary, normal-tension, and pseduoexfoliation) in either eye; age of older than 18 years; Snellen visual acuity of 20/40 or better; visual field MD of 2 post-screening visual fields differing by no more than 3dB for an MD of better than -6.0dB, or by no more than 4dB for an MD worse than -6dB; and the ability to give informed consent and to attend for the duration of the study. Exclusion criteria were the following: moderate/advanced visual field loss (MD worse than -10dB in the better eye or worse than -16dB in the worse eye) or a threat to fixation in either eye (a paracentral point with

sensitivity of <10dB in both the upper and lower hemifields) in either eye; IOP of >35 mmHg on 2 consecutive occasions in either eye or mean baseline IOP of 30 mmHg or more; inability to perform reliable visual field testing; poor quality structural imaging (assessed by Heidelberg Retina Tomography); cataract lens grading of more than N1, C2, or P1 according to Lens Opacities Classification System III grading; previous intraocular surgery (other than uncomplicated cataract extraction >1 year previous); and presence of diabetic retinopathy. (Garway-Heath et al., 2015; Garway-Heath et al., 2013).

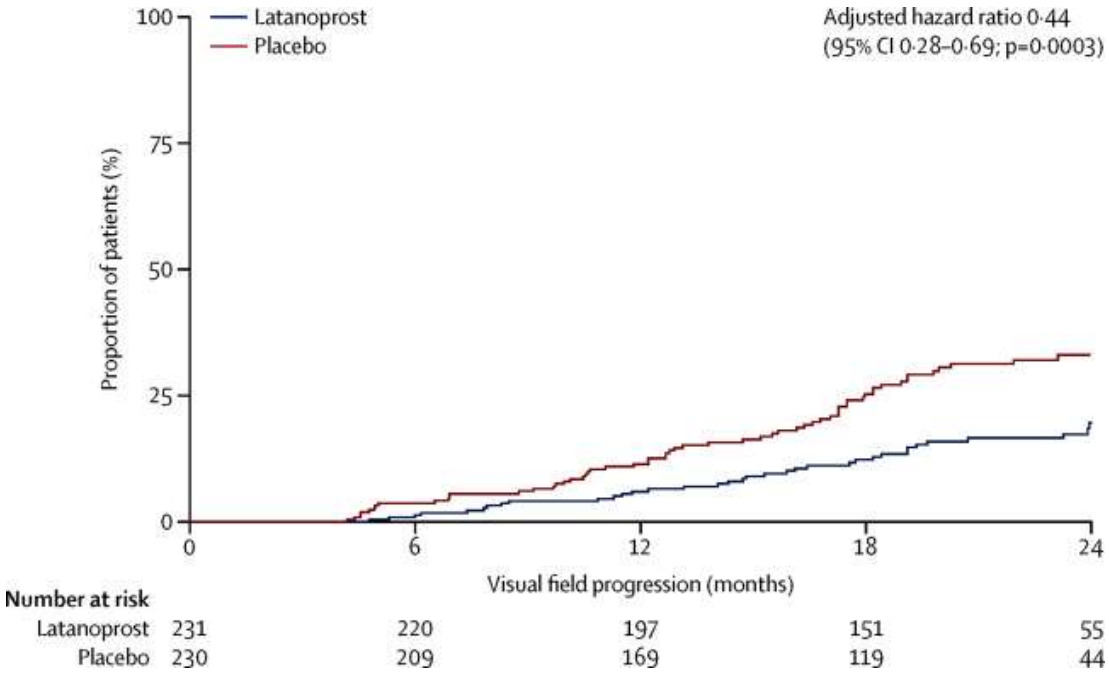

Figure 3.1: Kaplan-Meier failure estimates for visual field progression amongst patients in the UKGTS. Proportion of treatment patients found to be progressing at 6, 12, 18, and 24 months are represented by the blue line, proportion of placebo patients found to be progressing are represented by the red line.

The results of the UKGTS highlighted the magnitude of the treatment effect in the trial. Difference in IOP between the treatment and placebo group after 24 months was relatively small (2·9 mm Hg), due to the fact that untreated pressures at study entry were quite low. IOP-reducing drugs produce much smaller pressure reductions in eyes that start with low pressures than in eyes in which pressure is high. Still, the risk of progression was substantially lower in the treated group than in the group receiving placebo drops (adjusted hazard ratio 0·44 [95% CI 0·28–0·69]) (Figure 3.1). This finding

shows that IOP reduction is highly effective, and that every mm of pressure counts when treating patients with early glaucomatous disease (Leske et al., 2007).

PROMs were included as secondary outcome measures in UKGTS. PROMs were self-reported at patients' baseline and final visit and were administered by a trial researcher. In the event of a patient meeting the primary trial endpoint, PROMs were completed upon the patients' withdrawal from the trial. The PROMs used in UKGTS were as follows:

European Quality of Life in 5 dimensions (EQ-5D) is a classification of general health status (EuroQoL, 1990). EQ-5D assesses five attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. We used the three-level measure meaning each dimension has three possible outcomes: no problems, some problems, and severe problems. Patients with no problems across all five attributes will produce a five-digit health status code of 11111. Patients with severe problems will score 33333. Five-digit codes were translated into a single health state score using an existing scoring system which is generated from a UK population sample (EuroQoL, 1990). Included in the EQ-5D is a visual analogue scale (**EQ-5D VAS**) where patients are asked to score their own health between 0 and 100 (where 0 and 100 are worst and the best imaginable health). EQ-5D is the most commonly used general health PROM and is recommended in The National Institute for Health and Care Excellence guidelines for health economic analysis in the United Kingdom (Devlin & Brooks, 2017). Furthermore, following recommendations by the United States Public Health Service (Siegel et al., 1996), there now exists a large database of EQ-5D derived health statistics for the American population, too (Sullivan et al., 2005).

Short Form-36 (SF-36) is another general health instrument featuring 36 items across eight domains relating to: physical functioning, role limitation due to physical problems, emotional problems, bodily pain, general health, social functioning, vitality, and mental health (Ware & Sherbourne, 1992). Responses are made on Likert-type scales and the 36 individual items can be translated to give a global score for general health (ranging 0-100) where lower scores reflect poorer self-reported health. Following the International Quality of Life Assessment Project translation of SF-36 into several languages (Aaronson et al., 1992), this PROM has become frequently used in cost-utility studies (Hall et al., 2011).

Glaucoma Quality of Life (GQL-15) instrument has 15-items and is disease specific being designed to assess the impact of glaucoma on vision-related quality of life (Nelson et al., 1999). The GQL-15 was derived from an initial 62-item pilot questionnaire; the 15-items were included in the final instrument due to their strong relationship with visual field loss in glaucoma patients (Nelson et al., 2003). GQL-15 has four subscales: central and near vision, peripheral vision, mobility, and glare/dark adaptation. Scoring is based on five-point Likert-type scales where a response of 5 denotes severe difficulty and 1 indicates no difficulty. The measurement scale ranges from 15 to 75 where higher scores represent poorer vision-related quality of life. The instrument has been used in well-designed cross-sectional studies assessing the impact of glaucoma on patients' quality of life (van Gestel et al., 2010; Goldberg et al., 2009).

GQL-15 has previously been subjected to Rasch analysis to produce the 9-item **Glaucoma Activity Limitation (GAL-9)** PROM (Khadka et al., 2011). This instrument consists of a subset of nine items from the original GQL-15 and is considered to better reflect the effects of glaucoma on visual function (Khadka et al., 2011). GAL-9 has good external validity as scores from the instrument have been shown to correlate well with visual acuity and visual field scores. Furthermore, the GAL-9 is quicker to complete than the GQL-15 because it has fewer items (Khadka et al., 2011). In addition to our analysis of GQL-15 responses, we repeat the analysis on the items included in the GAL-9 for patients in the UKGTS.

For the data analysis, responses on the PROMs at baseline and exit were transposed into percentage scores. (The exit visit was at 24-months or, for progressing patients, at the visit when progression was confirmed). Differences between these scores were used to detect the degree of change in each PROM between first and last trial visit. For example, no change is indicated by zero and scores greater than 0% indicate worsening on PROMs, i.e. patients report more problems on exit from the trial than at baseline; negative values indicate improvement from baseline. Two-sample independent t-tests were used to determine whether there was a statistically significant difference in change on PROMs between the two trial groups (treatment and placebo).

Additionally, we assessed whether statistically significant differences in PROM responses could be observed between patients who remained stable during the UKGTS and those who experienced the primary trial endpoint. We included this additional analysis as it was anticipated that the largest difference in score for health-related and vision-related quality of life would be observed between these two patient groups.

3.3 Results

Complete baseline and exit PROM data were available for n=182 (79%) and n=168 (73%) of patients with follow-up data in the treatment and placebo arm of the trial, respectively. Average change in scores was similar for both the treatment and placebo groups across all the PROMs (Table 3.1). There were no statistically significant differences between the trial groups on PROMs relating to general health. Furthermore, there remained no statistically significant differences between the two groups on the glaucoma-specific PROMs. In addition, the distribution in the baseline to exit scores were strikingly similar between the treatment and placebo groups (Figure 3.2).

	Group			
PROM	*Treatment* *N = 182*	*Placebo* *N = 168*	Mean Difference [CI]	p-value
EQ-5D	1.7 (15.4)%	1.7 (10.6)%	0.0% [-2.8 to 2.8%]	0.98
EQ-5D VAS	2.1 (12.5)%	1.9 (12.0)%	0.2% [-2.8 to 2.4%]	0.88
SF-36	4.8 (19.8)%	5.0 (22.5)%	0.2% [-4.2 to 4.6%]	0.94
GQL-15	2.7 (7.7)%	3.2 (11.7)%	0.5% [-1.5 to 2.6%]	0.66
GAL-9	3.0 (8.5)%	3.2 (12.8)%	0.2% [-2.1 to 2.5%]	0.87
MD	-0.23 (1.9) dB	0.14 (2.0) dB		0.07

Change from baseline to exit is shown as a percentage (%). Percentages show the average amount of change on each PROM for treatment and placebo group. Positive percentages indicate worsening from baseline.

Table 3.1: Means (standard deviation) of percentage (%) change scores for the two trial groups (treatment and placebo) on PROMs between baseline and trial exit in the UKGTS. Mean (standard deviation) change in worse-eye mean deviation between baseline and trial exit in the UKGTS. More negative MD indicates improved scores from baseline.

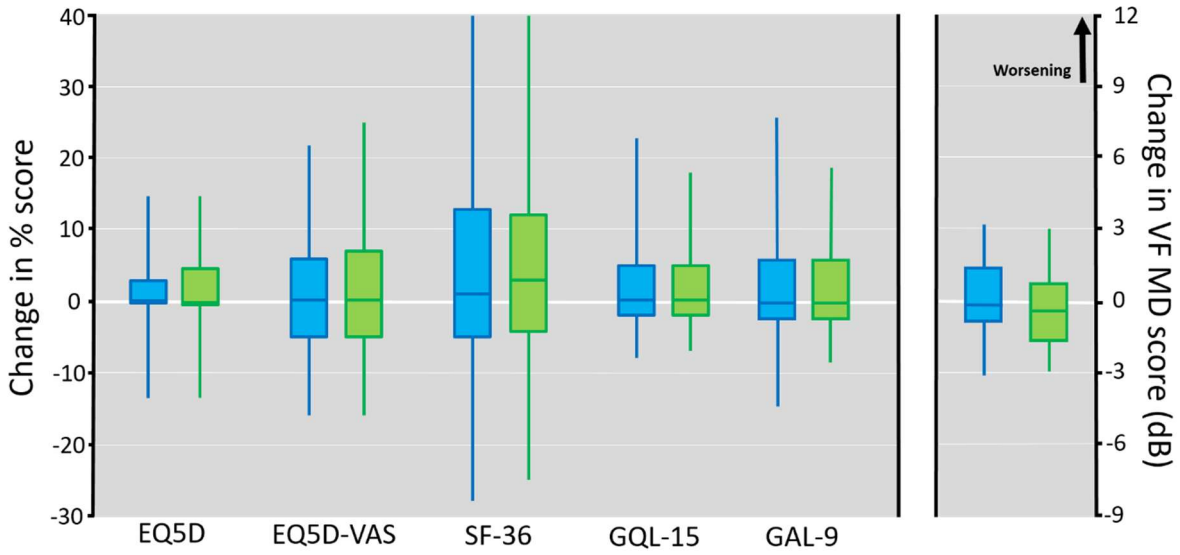

Figure 3.2: Boxplots on the left show change in scores between baseline and exit PROMs for patients in the placebo group (blue) and the treatment group (green) in the UKGTS. Positive scores (higher than 0) indicate worsening from baseline. Boxplots on the right show change in progressing/worse eye MD score between baseline and exit visual fields for placebo and treatment groups. (MD is a summary measure used to represent overall reduction in visual field sensitivity relative to healthy aged-matched observers. Lower MD values (more negative) are indicative of greater loss of vision). Boxplots give median, interquartile range, 5th and 95th percentiles (whiskers). Due to large variability in responses, 95th percentile is capped at 40% change for SF-36 analysis (SF-36 placebo 95th percentile = 54.6%; SF-36 treatment 95th percentile = 42.2%).

PROM data were not available at the exit visit for a proportion of patients in the UKGTS. Further analysis of those with missing data indicates that these patients had a similar profile to those with complete data (Table 3.2). Specifically, as determined through two-sample t-tests, there were no statistically significant differences between these two groups on baseline better eye mean deviation (MD) ($p = 0.12$), worse eye MD ($p = 0.90$), better eye visual acuity ($p = 0.44$), worse eye visual acuity ($p = 0.56$), and age ($p = 0.27$). As a group, patients without exit PROMs reported slightly worse average general and vision-related quality of life at baseline compared to those with exit PROMs. However, the magnitude of these differences was small; it might reflect some patients without exit PROMs being more likely to be people who were unwell at the start of the trial. For example, 32 patients had less than 21-months follow-up in the trial because of ill health and seven patients died during follow-up (Garway-Heath et al., 2015).

	UKGTS patients with PROMs *N = 350*	UKGTS patients without PROMs *N = 166*		p-value
MD (dB)				
Better eye				
Mean	-0.5 (1.2)	-0.8 (1.8)		0.12
Median	-0.5 [-1.3, 0.4]	-0.6 [-1.4, 0.3]		
Worse eye				
Mean	-4.2 (3.3)	-4.3 (3.6)		0.90
Median	-3.3 [-5.6, -2.0]	-3.4 [-5.7, -1.7]		
Best-corrected VA				
Better eye				
Mean	1.0 (0.21)	1.0 (0.24)		0.44
Median	1.0 [1.0, 1.2]	1.0 [1.0, 1.2]		
Worse eye				
Mean	0.9 (0.24)	0.9 (0.25)		0.56
Median	1.0 [0.67, 1.0]	1.0 [0.67, 1.0]		
Age (years)				
Mean	65.8 (9.9)	67.4 (11.9)		0.27
Sex				
Male	188 (53.7%)	85 (51.2%)		
Female	162 (46.3%)	81 (48.8%)		
Baseline PROM			Mean difference [CI]	
Mean				
EQ-5D	5 (7.2) %	5 (6.5) %	0 [0 to 3%]	0.53
EQ-5D VAS	81 (15.1) %	75 (18.7) %	6 [2 to 13%]	0.03
SF-36	77 (17.2) %	70 (19.9) %	7 [3 to 14%]	0.002
GQL-15	7 (8.9) %	11 (12.7) %	4 [1 to 10%]	0.003
GAL-9	7 (9.9) %	11 (14.7) %	4 [1 to 10%]	0.01

Data are n (%) or mean (standard deviation) or median [interquartile range].

Table 3.2: Comparison of baseline characteristics between patients in the UKGTS with PROM data (N=350) and those without PROM data at exit (N=166).

We assessed differences between stable patients (N=272) and patients with glaucomatous progression (N=78) as determined by the primary visual field outcome. Median (interquartile range) duration between baseline and progression confirmation visit was 465 (278, 553) days, in comparison to the 2-year (730 days) scheduled follow-up for patients remaining stable. No statistically significant differences were found between average responses from stable and progressed patients on PROMs relating to general health (EQ-5D, EQ-5D VAS and SF-36). Average differences between stable and progressed patients were statistically significant when assessing responses on glaucoma-specific PROMs (GQL-15 and GAL-9) (Table 3.3 and Figure 3.3). As a group, patients who had progressed on visual fields therefore reported a reduction in glaucoma-specific vision-related quality of life that was different to those who had remained stable on visual fields. Mean (95% CI) scores for the progression patients on the GAL-9 and GQL-15 was 6.5 (2.8–9.2) % and 3.9 (3.2–9.8) % respectively.

	Outcome			
PROM	*Stable*	*Progressed*	Mean Difference	
	N = 272	*N = 78*	[CI]	p-value
EQ-5D	1.5 (13.5)%	2.4 (12.5)%	0.9% [-2.5 to 4.3]	0.62
EQ-5D VAS	1.5 (11.8)%	3.6 (13.5)%	2.1% [-1.0 to 5.2]	0.23
SF-36	4.6 (20.3)%	6.0 (23.6)%	1.4% [-3.9 to 6.7]	0.65
GQL-15	2.1 (7.9)%	6.0 (14.3)%	3.9% [1.5 to 6.3]	0.02*
GAL-9	2.1 (9.1)%	6.5 (14.8)%	4.4% [1.7 to 7.1]	0.02*
MD	-0.22 (1.9) dB	0.55 (2.1) dB		0.003*

Change from baseline to exit is shown as a percentage (%). Percentages show the average amount of change on each PROM for stable and progressed trial outcomes. Positive percentages indicate worsening from baseline. * = significant at 0.05 level

Table 3.3: Means (standard deviation) of percentage (%) change scores for stable and progressed patients on PROMs between baseline and trial exit in the UKGTS. Mean (standard deviation) change in worse-eye mean deviation between baseline and trial exit in the UKGTS. More negative MD indicates improved scores from baseline.

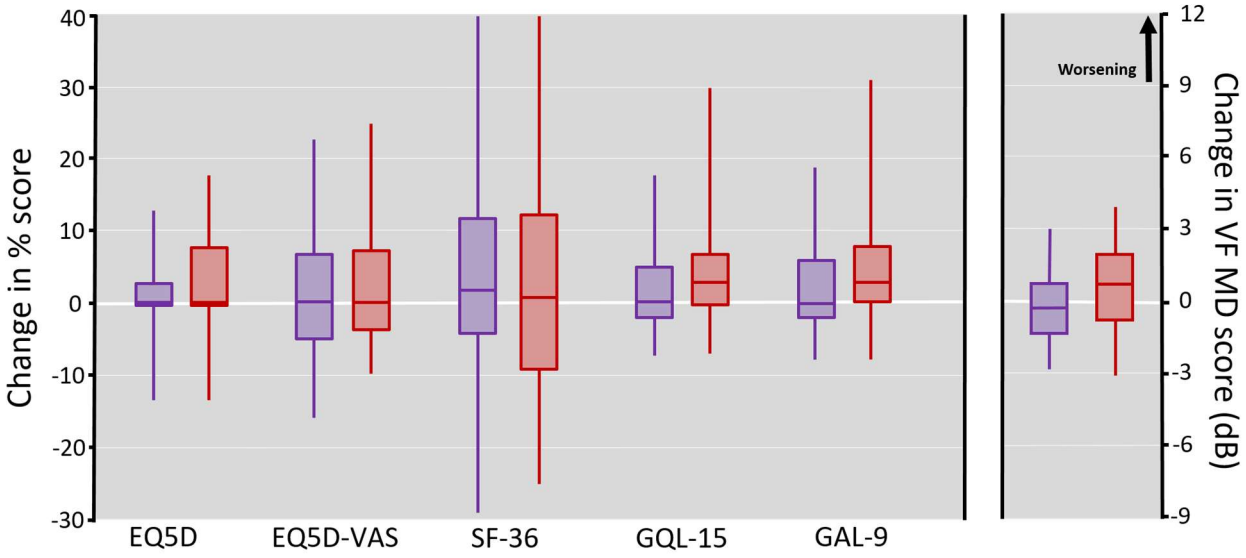

Figure 3.3: Boxplots on the left show change in scores between baseline and exit PROMs for patients remaining stable (purple) and patients with visual field progression (red) in the UKGTS. Positive scores (higher than 0) indicate worsening from baseline. Boxplots on the right show change in progressing/worse eye MD score between baseline and exit visual fields for stable and progression groups. Boxplots give median, interquartile range, 5th and 95th percentiles (whiskers). Due to large variability in responses, 95th percentile is capped at 40% change for SF-36 analysis (SF-36 stable 95th percentile = 42.4%; SF-36 progression 95th percentile = 53.8%).

3.4 Discussion

Results from this study show average changes in scores on general health-related PROMs (EQ-5D, EQ-5D VAS and SF-36) to be similar for patients receiving either Latanoprost or placebo eye drops in the UKGTS. Moreover, we did not find any evidence for differences between the two arms of the trial when analysing changes in PROMs specifically relating to vision and glaucoma (GQL-15 and GAL-9). Therefore, PROMs used in the UKGTS measured once at baseline and at 2-year follow-up (or final review, for those exiting early as a consequence of visual field progression) are not as sensitive as serial visual fields, taken over the same time course, in determining treatment differences in disease progression in a trial for glaucoma treatment.

There were other interesting findings from our study. Statistically significant differences were observed in average responses between stable and progressed patients on glaucoma-specific PROMs, but this was not the case for general health-related PROMs. This suggests general health-related PROMs are insensitive to treatment-induced changes in glaucoma progression, certainly in the population of patients represented in the UKGTS within the 24-month observation period. Another finding, not directly related to the aim of our study, concerns differences between GAL-9 and GQL-15. When comparing stable and progressing patients, GAL-9 yielded a marginally larger average effect (4.4%) when compared to the GQL-15 (3.9%). As such, we provide supporting evidence that the GAL-9 may be a satisfactory alternative to the GQL-15 when assessing glaucoma-specific vision-related quality of life. The GAL-9 has the added benefit of having fewer items and is therefore less burdensome for the patient to complete.

Our results have implications for trial design for glaucoma treatments. The UKGTS highlighted that a relatively short observation period could be implemented when adopting a sensitive change-from-baseline event criterion to identify visual field progression. This was made possible by frequent visual field testing and sensitive statistical methods where measurements that were repeatedly worse than baseline were flagged. Our results suggest that PROMs may not be sensitive enough to be used as outcome measures in glaucoma treatment trials, especially over a relatively short follow-up. Yet, it is important to note in the UKGTS, patients only completed PROMs at baseline and exit visits. The difference in mean deviation (a global measure, in the same sense as

a questionnaire score) of the visual fields taken at baseline and final review was also not sufficiently sensitive to identify differences between the treatment and placebo groups. Therefore, the explanation of the inability of the PROM scores to identify treatment differences is that either the PROM scores are insufficiently responsive to the small changes in disease observed over the short trial duration or that the scores are insufficiently precise, or both. Indeed, PROMs administered more frequently during the trial may have reduced the within person variability in responses and increase the likelihood of capturing significant changes. We are aware of at least two ongoing glaucoma trials that are doing this, albeit in different PROMS to the ones used in UKGTS (King et al., 2018; Vickerstaff et al., 2015). Still, the relatively small effects and large variability in our PROM data indicate that even repeat measures may not provide adequate trial power. It is encouraging that our chosen primary end point for the UKGTS, namely visual field progression, was sensitive enough to detect changes that are likely imperceptible to most patients in the early stage of the disease. It is important to note that our findings are based on the results of the UKGTS, where treated patients were compared to a placebo group. It is reasonable to suggest that the largest expected difference in scores between two arms of a randomised clinical trial would be when a placebo group is used. The fact that no differences were found when comparing treatment to placebo group in this study suggests that PROMs are very unlikely to be able to distinguish between patient groups in a trial comparing efficacy of two different interventions for glaucoma treatment, such as that in recent glaucoma clinical trials (Azuara-Blanco et al., 2016; King et al., 2018; Vickerstaff et al., 2015). However, in some of these cases the focus is not on patients with early glaucoma (King et al., 2018), and so greater differences between trial arms may be observed as vision-related quality of life is likely to decline faster amongst patients with advanced glaucoma, as discussed in Chapter Two (Jones et al., 2017; See supporting publications).

Longitudinal studies have revealed an association between visual field progression and changes in vision-related quality of life in glaucoma patients (Medeiros et al., 2015; Abe et al., 2016; Peters et al., 2015; Diniz-Filho et al., 2016). Yet, these studies have tended to use global or regional measures of visual field derived from binocular measures. We are unaware of any longitudinal studies reporting changes in quality of life measures that are associated with progression events detected at a visual field test location level using GPA software. Ultimately, it makes sense that trial endpoints are

aligned to relevant and meaningful outcomes for the patient, and we have highlighted that disease-specific instruments, like GAL-9 and GQL-15, can track visual field loss amongst glaucoma patients. Moreover, it remains important that all stakeholders are considered when deciding on outcome measures in clinical trials, and that includes the patients themselves (Dean et al., 2017).

Other observations on our results are noteworthy. Average changes in PROMs, where they existed, were small and the variability in response between participants was large. For example, the average 6% decline on the GQL-15 in the N=78 patients who were progressing on visual fields is equivalent of a change from 'no difficulty' to 'a little bit of difficulty' on just four of the 15 items on the GQL-15. This small average change in vison-related quality of life suggests that patients experiencing the visual field endpoint do not perceive large changes in visual function, in this cohort with glaucoma mostly at its earliest stage. This is an interesting finding because it has been suggested that placebo-controlled clinical trials for glaucoma treatment can be harmful for those randomised to the placebo arm (Wegner, 2015). However, our findings certainly indicate that vision-related and health-related quality of life was similar between patients in the placebo group to those randomised to treatment over the course of the trial. In the case of the UKGTS, all patients were monitored closely over a short trial duration and the criterion for visual field deterioration was proven to be very sensitive. On average, patients progressing, based on visual fields, experience a small or unnoticeable reduction in vision-related quality of life. They certainly do not, on average, experience a change in general health as measured by the general-health PROMs considered in our study and this is particularly noteworthy. These findings support an argument for close monitoring being an alternative to medical treatment in the early stages of the disease, an observation made from the results of previous clinical trials (Heijl et al., 2002; Anderson et al., 1998). As no statistically significant differences in PROM scores were observed between the treatment and placebo group in UKGTS, our findings might have implications for how health-related and vision-related quality of life are assessed in clinical trials. More objective or 'real-world' assessments of visual disability are emerging, and these have potential for use as trial outcomes that are meaningful to the patient. One such measure, the Assessment of Function Related to Vision (AFREV), requires users to perform visual tasks such as findings objects, using everyday technologies, and reading under various illuminations (Altangerel et al., 2006). If used as an outcome

measure, tools such as the AFREV may yield more discernible differences between treatment groups in glaucoma clinical trials, but this remains speculation until tested. An added advantage of such objective measures is that, unlike PROMs, they are less reliant on the functional literacy of the patient. Offering definitive guidance on the use of PROMs or visual fields, or a combination of the two, as outcome measures for glaucoma trials is beyond the remit of this study. These issues are complicated because, for example, PROMs are derived from the individual, who has two eyes, and the visual field outcome is derived from just one eye (the first showing progression), and in the UKGTS just 11% (n = 10) of progressing patients had visual field progression in both eyes. PROM performance in glaucoma is likely driven by the least affected eye but this is dependent on the stage of glaucoma (Skalicky et al., 2016; Arora et al., 2013); in the UKGTS, almost 50% of participants had glaucoma in only one eye. Furthermore, the visual field progression outcome occurred in one eye only in almost 90% of participants with identifiable progression (94 of 461 subjects) and in 73% of these, the progression was in the worse eye. Thus, the person-level PROM outcome would be expected to be less sensitive to glaucoma deterioration than eye-based measures of visual function. For example, standard automated perimetry will detect changes in sensitivity that may be unnoticed by the patient, whereas PROMs will likely be more responsive to central visual field loss. This does not mean that PROMs do not have a role in treatment trials; they may have a more important role in identifying adverse (or even beneficial) effects of interventions on the person that they have in identifying disease modifying effects.

The study was not without limitations. In some cases, not all patients completed PROMs at baseline or exit from the trial and so no comparable data were available for analysis. Yet, patients with and without PROM data had similar demographic and visual function profiles. One key limitation comes from patients possibly being aware of the status of their glaucoma progression (stable or worsening) at the time of completing exit PROMs. This is certainly true for patients withdrawn early from the trial because visual field progression had occurred. If, for example, a patient was told they were exiting the trial because their clinically measured vision was getting worse, then that would likely influence self-report of quality of life. If this were the case, one might expect knowledge of glaucoma progression status to affect general health-related, as well as vision-related, quality of life, but there were no differences in the EQ-5D or SF36 between those who progressed and those who did not. As previously discussed, the design of the UKGTS

meant that patients completed PROMs at only two time points. This is obviously different to the frequent collection of visual field data (primary outcome). Our results are also limited to apply to only a UK population of newly diagnosed patients, most of whom were at the earliest stage of the disease. We cannot say how PROMs may change over a period of 24-months in people with more advanced disease. Patient's vision-related quality of life may decrease more quickly when visual field loss is already quite advanced (Jones et al., 2017). A further limitation of this study is the fact we did not compare differences in groups per PROM item, but rather we used global scores for PROMs overall. However, we did compare scores between the original GQL-15 and the Rasch analysed variation, the GAL-9, and found the latter to be more sensitive to glaucomatous disease progression, as seen by the greater average difference in PROM change score. This would suggest that the Rasch analysis of the GQL-15 had already identified items that were most sensitive and relevant to a glaucoma population. Yet, it remains true that specific items on PROMs used in the UKGTS may be better able to distinguish between patient groups. For example, complaints about lighting conditions are common for patients with glaucoma (Burr et al., 2007; Nelson et al., 1999). Specifically, having difficulty with glare and light adaption have been ranked as the most problematic symptom of glaucoma; more so than trouble with mobility, reading, and socialising (Nelson et al., 1999). Furthermore, problems with glare and lighting are frequently reported in patients with even mild cases of glaucoma (Burr et al., 2007), and glaucoma suspects with impaired scotopic vision are more likely to have signs of early optic nerve injury (Glovinsky et al., 1992). These findings suggest that difficulty with light adaption may be one of the earliest symptoms presented in patients with glaucoma, thus PROM items relating to dark and light adaptation may be particularly sensitive at detecting changes between patient groups. This idea is being explored further in a large-scale project to assess the impact of lighting conditions in patients with glaucoma, and the author of this thesis is currently involved in a systematic review of the literature in this area (Available Online: www.crd.york.ac.uk/prospero/. Review ID CRD42018118953).

In conclusion, patients randomised to treatment or placebo in the UKGTS returned similar responses to PROMs at baseline and final visits of the trial. It is accepted that no single PROM covers all aspects of patients' vision-related quality of life (Somner et al., 2012), and our findings at least emphasise the importance of appropriate PROM selection when designing and implementing clinical trials. Even if PROMs cannot capture

the disease modification effect of an intervention, that certainly does not mean that they are not useful if they can capture other consequences of an intervention including, for example, side effects or inconvenience of treatment regimens. In the UKGTS differences in PROM responses only emerged when comparing stable and progressed patients on instruments that were specific to glaucoma. As such, we suggest PROMs alone, administered at the start and end of a 24-month trial assessing disease progression, may not be sensitive enough to be used as the primary endpoints in glaucoma clinical trials assessing disease progression.

Chapter Four - Monitoring glaucoma patients in the hospital eye service

Once diagnosed, patients with glaucoma require lifelong monitoring, often within the hospital eye services. Repeated clinic visits can pose as a significant burden for patients living with chronic disease, where long waiting times and financial constraints can impact on glaucoma patient's quality of life (Kotecha et al., 2015a; Kong et al., 2014). Glaucoma patients have described significant concerns about aspects of their care, including delayed appointments, long waits to see a professional at each appointment, and rushed consultations. A report from the RNIB entitled 'Saving money, losing sight' (RNIB, 2013) highlighted the key aspects of glaucoma monitoring patients were concerned about:

> **"The eye hospital clinics are total chaos! The appointment time bears no relationship to when you will be seen. I find it hard to sit for hours not knowing what is happening"**
>
> **"I knew delays would lead to permanent damage that could never be reversed – I started to think I would never gain access to what I needed to save my sight before I lost it forever"**
>
> **"When the specialist says he wants to see you in three months, you should see him in that timeframe, instead of having to wait seven months during which time your condition has worsened"**

Virtual glaucoma clinics may offer one solution for the concerns about hospital capacity. As described in section 1.4.7, a virtual glaucoma service may improve in-patient capacity and reduce hospital delays, subsequently reducing the burden of monitoring for the patient. However, it is important to consider whether a virtual glaucoma service is a viable means of monitoring patients, and this is the focus of this chapter. Although quality of life is not directly measured in this study, the findings may have significant implications for the way in which glaucoma patients are monitored in the hospital eye service, and consequently affecting patient quality of life.

The work presented in this chapter has formed a paper published in British Journal of Ophthalmology (Jones et al., 2017); see list of supporting publications. The co-authors of this work are David Crabb (DC), Susan Bryan (SB), Marco Miranda (MM), and Aachal Kotecha (AK). Access to the data was approved by AK, the Caldicott Guardian, and Information Governance Lead at Moorfields Eye Hospital NHS Foundation Trust. Help with data extraction came from MM. Help with data analysis and plotting of the

'Hedgehog' plots came from SB. Data extraction and analysis were performed by Lee Jones (LJ). The paper was written by LJ, and reviewed, edited, and approved by all authors. The work presented in this chapter has also been presented as a poster presentation at the British Congress of Optometry and Vision Science (Plymouth, UK, 2017); see list of supporting publications.

4.1 Introduction

The UK National Health Service (NHS) is facing unprecedented challenges. Although overall life expectancy is increasing, with it comes a greater prevalence of disease in the population (Murray et al., 2015), and chronic disease management remains a significant burden on the NHS (Lewis & Dixon, 2004). There is a need for the NHS to redesign its services to make a more efficient healthcare service provider.

A drive exists for the NHS to make more use of information technology (IT) (Department of Health, 2016). One such example is the development of virtual clinics, which remove the face-to-face doctor-patient consultation. Within the hospital eye service (HES), virtual clinics have not only been found to provide valuable additional out-patient capacity, but can also streamline referral rates, reduce costs, and improve the patients' health care experience (Kotecha et al., 2015a; Trikha et al., 2012; Ross et al., 2016; Vardy et al., 2014). Improvements in disease detection by primary eye care service providers have meant that the HES has become one of the busiest health care providers in the UK (Vernon et al., 2011; Edgar et al., 2010; Khan et al., 2012; de Silva et al., 2013). As a result, the introduction of new methods to assist with the monitoring of patients with chronic ocular disease in the HES is a high priority.

Virtual clinics offer a viable means of monitoring glaucoma patients (Trikha et al., 2012; Rathod et al., 2008; Wright & Diamond, 2014; Clarke et al., 2017). To date, most studies have focused on the accuracy of disease staging, as well as patient satisfaction, cost reduction, and appointment durations (Kotecha et al., 2015a; Clarke et al., 2017; Kotecha et al., 2015b. An important safety aspect of virtual clinics is whether disease progression can be identified and acted on effectively. By doing so, scrutiny can be placed on the extent to which virtual clinic patients differ from patients in consultant-led appointments when performing the same tests. This type of analysis can be conducted through an audit-style assessment using large scale data.

Following the development and expansion of the Internet, as well as the advent of new and innovative technologies, the use of large scale data, or "big data", has increased dramatically in recent years (Raghupathi & Raghupathi, 2014). Put simply, large databases from routine services can be used to compare individual or population results of patients attending a single hospital, practice, or clinic. This method has been used recently in the field of ophthalmology (Boodhna & Crabb, 2015; Sparrow et al., 2011).

A virtual clinic must be effective at identifying patients who have become unstable and are in need of closer observation. One method to assess this aspect of virtual clinics is to use large scale data collected from consultant-led appointments as benchmarks for patient's measurement results. This is the idea explored in this current work.

In this study, we examine the effectiveness of a virtual glaucoma monitoring service (GMS) at identifying unstable patients requiring closer observation. In addition, we assess whether "big data" analysis can be used to identify patients achieving visual field test scores outside of the expected range.

4.2 Methods

Following authorisation from the Caldicott Guardian and Information Governance Lead at Moorfields Eye Hospital NHS Foundation Trust (MEH), anonymised visual field results from the Humphrey Field Analyser (HFA; Carl-Zeiss Meditec, Dublin, CA, USA) of patients attending the glaucoma monitoring service (GMS) were analysed. The GMS, and criteria for patient inclusion into the service, is described in a previous publication from our group (Kotecha et al., 2015a). In brief, clinical examinations of 'early' and 'moderate' disease stage glaucoma patients are carried out by trained ophthalmic technicians and data are reviewed by two consultants and a senior glaucoma specialist optometrist on a different day for clinical management decisions (Kotecha et al., 2015a).

Inclusion criteria required patients to have at least two visits to the GMS no less than 4 months apart. The first 250 patients who entered the GMS since its start in 2014 who fulfilled this criterion were analysed. This sample represents approximately 15% of patients attending the GMS at the time of data collection.

Visual field data were manually downloaded from two (of two) HFAs located in the virtual clinic (performed by LJ). This process involved searching both machines for all clinic visits for each of the 250 patients included in the study. Once measurements were located for both eyes on all visits to the virtual clinic, the Portable Document Format (PDF) outputs were downloaded and individual data were inputted into a spreadsheet. These data were restricted to patient's age, test date, test eye, test reliability, and mean deviation (MD). The latter is conventionally used in clinics; it is a summary measure of the overall reduction in visual field sensitivity relative to a group of healthy age-matched observers, with more negative values indicating a worse visual field. We used patients' worse eye (based on MD) at their first GMS visit as our study eye. In addition to the manual data extraction, the same PDF outputs underwent the optical character recognition function using a purpose-written program authored in MatLab 2016b (Mathworks Inc.). Optical character recognition is a technique of translating handwritten, typewritten or printed text characters to a machine-encoded text. It is widely used as a form of data entry from printed paper data records, such as clinical computerised documents. The process involves an image being captured by digital camera and is converted into a suitable form required by the machine. Thus, it allows for digital texts to be electronically edited, searched, stored more compactly, displayed on-line and used

in machine processes (Chaudhuri et al., 2017). Equivalence was assessed between the manually collated visual field spreadsheet and the computerised data download. In the few instances where discrepancies occurred, the original raw data was revisited and the correct value was input into the spreadsheet.

Data Analysis: We used the difference in MD between GMS patients' baseline and second appointment as a surrogate of visual field stability. Large differences would suggest a change in the visual field, or poor repeatability.

Limits were defined for change in MD from a database of 473,252 visual field records (the reference database). These data are described elsewhere (Boodhna et al., 2015), and were pooled from 88,954 patients from four centres in the United Kingdom: Moorfields Eye Hospital NHS Foundation Trust, London; Cheltenham General Hospital Gloucestershire Eye Unit; Queen Alexandra Hospital, Portsmouth; and the Calderdale and Huddersfield NHS Foundation Trust. Only patients tested using the 24-2 testing algorithm were included, resulting in a total of 83,794 patients.

Patients attending the GMS are all experienced in perimetry, but this may not necessarily be true for patients within the reference database. Thus, we excluded the first ever visual field test for patients within the reference database to allow for perimetric 'learning'. Furthermore, eliminating the first visual field in a patient's series would also exclude patients from the reference database who had a single, exploratory visual field, thereby increasing the confidence that patients remaining in the reference database who had at least 2 subsequent visual fields were being monitored for glaucoma. In this database, 41,048 patients (49%) were excluded based on this criterion. In addition, we restricted the age (minimum age of 20 years) for the reference database to ensure that these patients were age-related to patients seen in the GMS. Duration between appointments in the reference database was restricted to between 4 and 24 months to ensure similar time intervals for follow up between the two groups. After applying these criteria, 22,124 patients remained in the reference database. We then grouped the average MDs by visual field defect severity using bins of 1dB width. We did this because visual field measurement repeatability is strongly associated with visual field severity (Russell et al., 2013). The 5^{th}, 25^{th}, 75^{th} and 95^{th} percentile of the distribution of difference were then derived and plotted. Points were connected using a locally weighted smoothing operator (LOESS) to create a colour coded chart for the 50% and 90% limits

of change for MD in the reference database (See figure 4.1). We would, for example, expect 10% of GMS patients to have repeat MD differences outside of the latter limits. By using this method, GMS patients who had visual field results that were markedly different to those in the reference database (i.e. outside the 90% normal limit) could be identified.

For the second part of the analysis, we included a subset of the GMS patients who had attended three or more appointments (N=158). GMS patients with three visual fields were compared to patients in the reference database with three visual fields; this was repeated for patients with four and five visual fields. Where two visual fields were conducted within 4 months, the patients' next measurement in their visual field series within our inclusion criteria was used. Simple linear regression was used to calculate the rate of visual field progression (MD dB loss per year). Regression lines for the reference database were plotted using a novel data visualisation tool, the *Hedgehog Plot*. This tool allows us to visualise the progression rates for all patients simultaneously. The reference database was used to determine the 90% limits by computing the 5^{th} and 95^{th} percentiles of the estimated slopes. The regression lines for the GMS patients were then superimposed onto the Hedgehog plot and eyes which were found to be outside of the calculated limits were flagged.

The clinical management decisions for all 250 GMS patients at the time of their most recent field were also collected. All statistical analysis was done in R (www.R-project.org).

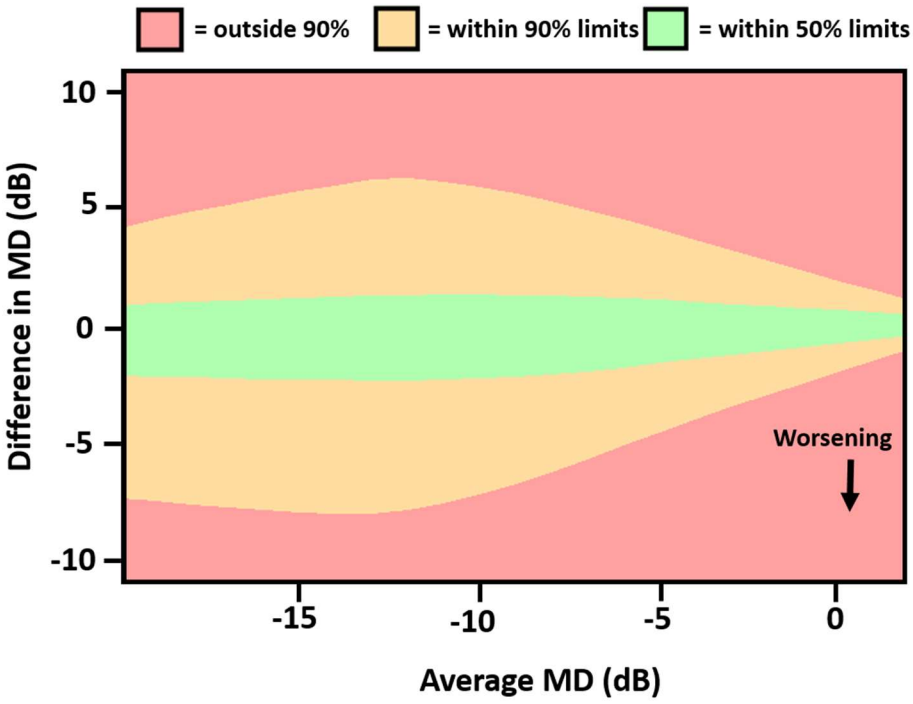

Figure 4.1: Distribution of expected limits for size of difference in MD (dB) index between two appointments in the reference database (N = 22,124) based on the patient's average MD. Areas at the upper and lower most part of the plot (red) show results outside of 90% normal limit. The lower most part of the plot indicates worsening visual field results.

4.3 Results

Median (interquartile range; IQR) age of GMS patients at first visit was 65 (54, 72) years. Median (IQR) MD for GMS patients' worse eye at baseline was -1.5 (-3.1, -0.3) dB. Median (IQR) number of months between the first and second GMS clinic appointments was 12 (10, 12) ranging from 4 months to 21 months. Average MD of the first and second appointments of the 250 GMS patients ranged between +1.6 dB and -18.9 dB (median -1.4 (-3.0, -0.4) dB). Median (IQR) age of patients from the reference database was 67 (57, 76) years.

Of the 250 GMS patients, 12 (4.8%; 95% confidence interval [CI] 2.5 to 8.2%)) recorded values outside the 90% limits. This proportion was less than the expected value of 10% and was statistically significant ($p = 0.003$). (A post-hoc power calculation confirms our study to have had an adequate sample size. A total of 4.8% outside the 90% limit returns a power (beta) value of 0.86 when alpha is set at 0.05 and N = 250; Minitab 17 Statistical Software (2010); www.minitab.com).

Figure 4.2 shows the results of the GMS patients (points) compared to the reference database. We split the GMS patients into three equally sized groups. Plot A ranges from -18.9 dB to ≤ -2.4 dB (83 GMS patients), plot B ranges from > -2.4 dB to ≤-0.8 dB (84 GMS patients), and plot C includes patients > -0.8 dB (83 GMS patients).

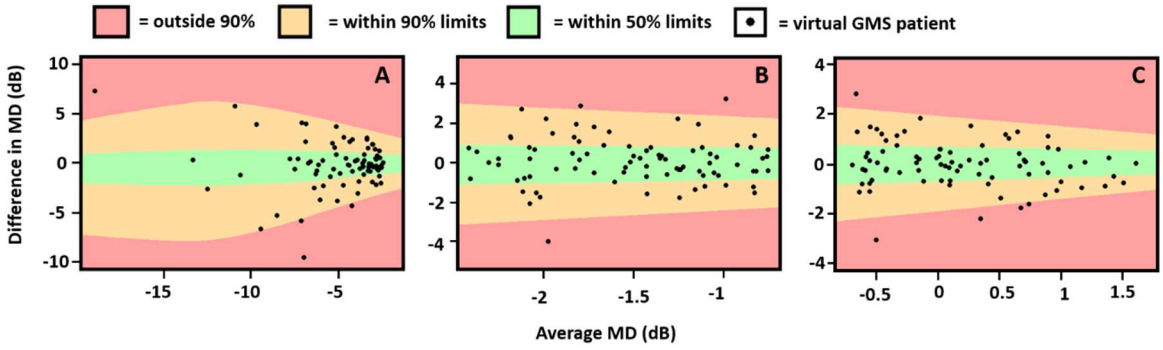

Figure 4.2: Virtual GMS patient (points) data compared against the reference database. Our total sample (N=250) is divided into 3 groups based on average MD. Plot A ranges from -18.9 dB to ≤ -2.4 dB (83 virtual GMS patients), plot B ranges from >-2.4 dB to ≤-0.8 dB (84 virtual GMS patients), and plot C includes patients > -0.8 dB (83 virtual GMS patients).

Figure 4.3 shows the rate of visual field progression for patients in the reference database. Each line represents an eye, with the length of the line indicating the length of follow-up. The location of the line is aligned to the patient's age (x-axis) and severity of initial loss (y-axis); steeply declining lines indicate rapidly progressing eyes. After applying our inclusion criteria, 18,414 reference database patients were included.

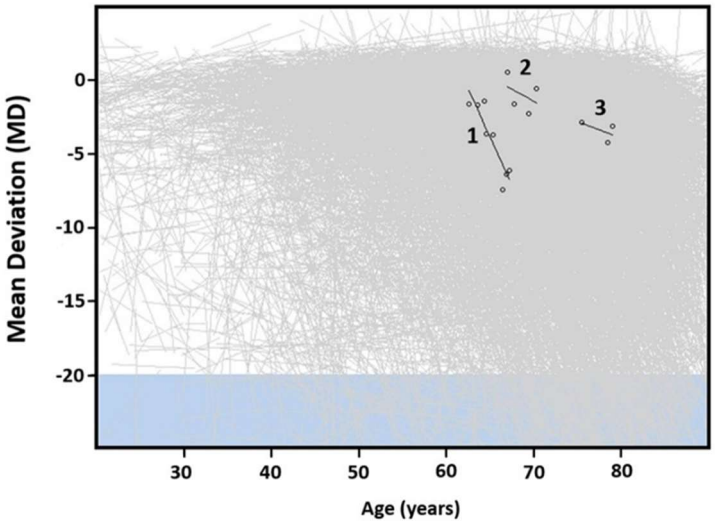

Figure 4.3: Hedgehog plot showing the rate of visual field progression in the reference database (N=18,414). Three patients have been highlighted. For each patient, a point represents a score on the visual field test and patients' age at time of test. A regression line is fitted for each patient using all of the points in their series. Steeply declining lines indicate faster visual field progression. The blue shaded area denotes likely visual impairment. In this example, patient 1 has the most visual field tests in their series and shows a faster rate of progression than patient 2 or 3.

In Figure 4.4, GMS patients progressing (red lines) and improving (green lines) faster than the 90% limit in the reference database with the same number of visual fields are highlighted. Three (1.9%; 95% CI 0.4 to 5.4 %) patients are flagged as having visual field changes outside of expected limits.

Table 4.1 shows the diagnoses of the 14 patients identified by both analyses as having visual field MD changes outside the 90% limits of the reference database. Twelve patients were identified in the first analysis, three in the second analysis, however one patient was identified in both analyses, and hence a total of 14 patients were identified across both analyses. Nine patients performed worse than patients in the reference database, although five of these had a positive MD at their baseline GMS visit. Of the

remainder, one patient was judged to be progressing by the GMS reviewer, one patient had a retinal arterial occlusion unrelated to their glaucoma, one patient was exited from the GMS due to suspected unreliable visual field performance, and one was deemed stable by the GMS reviewer and kept in the clinic.

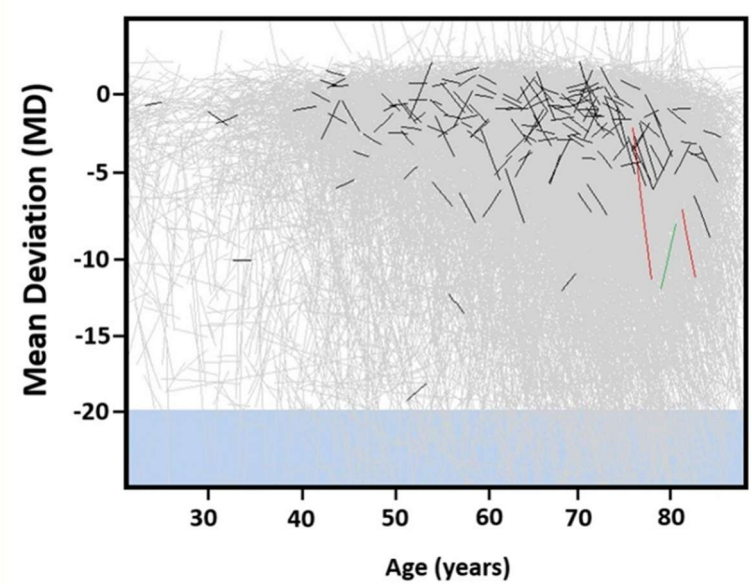

Figure 4.4: Of the 250 virtual GMS patients, 158 (63.2%) had 3 or more visual fields in their series. These patients are superimposed on the reference dataset Hedgehog Plot. Grey lines show rates of progression for patients in the reference database. Darker lines show virtual GMS patients. Red lines highlight the virtual GMS patients outside the 90% limits for progression. The green line highlights the virtual GMS patient outside the 90% limits for 'improvement'.

Age (years)	Diagnosis	MD at first GMS visit (dB)	Progressing (P) or 'improving' (I)	GMS outcome recorded in notes
49	OHT	+1.03	P	Remains in GMS; 12-month review
52	OHT	-22.59	I	Exited GMS in January 2015; noted to be poor visual field performer; moved to consultant clinic for further follow up.
63	OHT	-2.60	I	Remains in GMS; 9-month review
65	OHT	-2.08	I	Remains in GMS; 12-month review
67	OHT	+1.45	P	Remains in GMS; 6-month review
71	OHT	+1.56	P	Remains in GMS; 12-month review
75	OHT	+0.03	P	Remains in GMS; 12-month review
77	OHT	-2.02	P	Remains in GMS; 18-month review
78	OHT	-3.24	I	Remains in GMS; 12-month review
42	Glaucoma suspect	+1.55	P	Remains in GMS; 12-month review
55	Glaucoma suspect	-4.17	P	Exited GMS April 2016; discharged from service- no evidence of glaucoma, poor visual field performer.
77 *	Glaucoma suspect	-2.16	P	Retinal arterial occlusion; detected in March 2016 (i.e. pre-glaucoma service visit); glaucoma stable.
80	Glaucoma suspect	-13.78	I	Exited GMS June 2016; no evidence of glaucoma, poor visual field performer; moved to consultant clinic to assess suitability for discharge from glaucoma service.
82	POAG	-7.97	P	Exited GMS April 2016 as evidence of progression. Review in consultant clinic.

Key. MD = mean deviation, GMS = glaucoma monitoring service, OHT = ocular hypertension, POAG = primary open angle glaucoma.

Table 4.1: Outcomes of GMS patients identified as falling outside of the 90% limits in the reference database. * = shown to be significantly progressing with both analyses 1 & 2.

4.4 Discussion

Our study exploited a "big data" approach to investigate whether patients in a GMS score similarly on a measure of vision loss (i.e. visual field MD) to patients who attend consultant-led appointments (reference database). Our results show the difference in MD values between two hospital appointments for patients attending the GMS is similar to those in the reference database.

Using "big data" we created ranges of expected change in MD over a similar follow up interval, using patients with a similar profile to those attending the GMS. Our findings also showed that 12 patients in the GMS scored outside the expected range on the visual field test. The proportion of GMS patients outside the expected range (4.8%) is smaller than the 10% (25 patients) we allowed for. Similarly, when compared to the reference database, there were fewer GMS patients with unusually fast progression. The results of our study indicate that the number of patients in a GMS performing better or worse than expected on the visual field test is smaller than anticipated.

The results of our study are relevant to current clinical practice with regard to monitoring patients with glaucoma. Our findings suggest that patients attending a GMS are no 'worse-off' than those attending the standard-care appointments. Specifically, when using visual field data from a large reference database as benchmarks for expected changes in MD score, GMS patients' visual field test results tended to be as expected. In the few cases where GMS patients' MD scores were outside the expected results, further analysis on these patients was carried out. It was found that 5 patients scoring outside the expected results had been highlighted as 'improving'. Of the 7 patients showing a worse performance compared to the reference database, 3 had been picked up by the GMS reviewer, with the remainder being deemed stable. It should be noted that those deemed clinically stable had a diagnosis of either ocular hypertension or suspected glaucoma with no significant visual field defect.

A strength of our study is the number of patients we included in our analysis. Access to a wealth of visual field entries in the reference database, even after applying sensible selection criteria, meant that we closely matched patients in the GMS to patients attending standard, consultant-led appointments. The total number of patients in the reference database for the first part of our analysis was 22,124 and 18,414 for the second

part. These large numbers allowed limits for variability to be stratified by disease severity (Russell et al., 2013; Chauhan et al., 1993; Henson et al., 2000)

It should be noted that the number of patients in the reference database used to create our expected limits is not equal across all average MD bins on the x-axis of our plots. For example, the number of reference database patients creating the -15 dB average MD limit was 257, whereas the number of patients creating the -5 dB average MD limit was 1,350. However, we wished to include as much data as possible and so, given that there were simply more patients with average MD of -5 dB than -15 dB, this disparity is to be expected. Additionally, the -15 dB limits were where the fewest reference database patients were included (N=257), but this number of patients remains substantial. A further point to consider is that in Figure 4.4 it appears older patients have less stable visual fields in the GMS. This could be due to these patients presenting at a later stage in the disease, precipitating more visual field variability, or they have had the disease for a longer period of time, or they are worse test takers.

A limitation to our study is the inclusion criteria we used to construct the reference data percentiles (Figure 4.1). We match GMS patients to reference database patients using baseline MD, age, and interval between clinic visits. We did not have access to reference database patients' diagnoses. GMS patients are a highly selected sub-group of glaucoma patients attending the Moorfields Eye Hospital glaucoma outpatient service; some reference database patients would not be suitable for virtual monitoring. For example, glaucoma patients with a coexisting ocular comorbidity would not be suitable for GMS but may be present in the reference database and this represents a possible confounder. Furthermore, we anticipated that patients in the GMS would be experienced in performing the visual field test. However, some GMS patients appeared to show improvement in their MD scores; these patients may be unreliable at performing the visual field test or are continuing to have perimetric learning effects despite being experienced test-takers. We did not have data for variables such as intraocular pressure, or optic nerve assessment which may influence progression. This is a key limitation. Further analysis adjusting for these factors would be a valuable addition to the literature. Patients in the "big data" (reference) group are simply defined as having measurable glaucoma-like visual field loss who are attending glaucoma clinics. Therefore, for example, we cannot rule out some patients having optic neuropathies that produce glaucoma-like visual field deficits, but the number would be insignificant given the sheer

number of records in the reference database. Moreover, for example, patients with sudden onset retinal vein occlusions or unstable aggressive glaucoma may skew the expected parameter limits in the reference database. However, as the reference database is comprised of patients attending glaucoma clinics, the number of those with visual field loss due to non-glaucomatous comorbidities is likely to be smaller than that reported in general population prevalence estimates (Mitchell et al., 1996). But these examples do highlight some limitations of the "big data" approach. A final limitation surrounds the method used to assess change between visual fields. Here we have used a visual field index (MD) and alternative methods using all the points in the visual field might offer more sensitivity to change (Bryan et al., 2013).

The average number of appointments for GMS patients in our study was three. Further analysis where patients attending a GMS are followed longitudinally may provide more information regarding the suitability of virtual monitoring. Given that GMS are a relatively new addition to the HES, this idea should be revisited in future research.

To our knowledge, this is the first study that utilised “big data” to evaluate outcomes of patients in a GMS. The utility of pooling large databases together to identify trends and also predict future risks to health is recognised elsewhere (Bradley, 2013). In the presented study, we have utilised “big data” to assess whether a new model of service delivery results in equivalent outcomes to that of the standard out-patient model, and for the metric we used (i.e. MD), we found that it did. The digital nature of visual field test results lends itself to “big data” analysis. Still, the visual field result is but one measure of glaucoma status. However, we feel that this study has shown the potential of using “big data” in the ophthalmology setting to confirm the equivalence of care between a new and standard model of service delivery.

Chapter Five - The experience of surgical intervention for advanced glaucoma

Researchers have recognised the unique impact ophthalmic surgery can have on patients' psychological wellbeing (Nijkamp et al., 2004; Marback et al., 2007). Fear of blindness following trabeculectomy glaucoma surgery have been reported amongst patients with advanced-stage of the disease (Cross et al., 2009). Moreover, patients with early glaucoma and good binocular vision have also cited vision loss as a result of surgery as a primary concern (Janz et al., 2001). Advanced glaucoma patients undergoing surgery on the better or 'only' eye represent a unique cohort of patients in the hospital eye service who may have experienced unprecedented challenges in their treatment journey, and can provide detailed insight into the experiences of advanced glaucoma and surgical intervention.

There are currently no standardised definitions for what constitutes an 'only eye', but when considered from both a patient and surgical perspective, one could use characteristics which focus on the impact of loss of the eye. The practical working-definition used for this study was:

> "An eye was considered an 'only eye' when significant loss of vision in this eye would be deemed life-changing with profound impact on the quality of life by both patient."

The purpose of this study was to learn about the surgical experiences of patients undergoing only-eye surgery for glaucoma. In addition, as these surgeries can be considered as high-stakes, as negative outcomes may result in visual disability for the patient, experiences of surgeons performing only-eye glaucoma surgery were also explored. Both patients and surgeons were asked to recall their experiences of these high-stakes procedures using semi-structured interviews. For the purpose of structuring this chapter, the review of literature, data interpretation, reporting of findings, and discussion of results are divided into two sections, the first relating to surgeon perspectives (Section 5.1 to 5.4), and the second relating to patient perspectives (Section 5.5 to 5.8).

The co-authors of this work are Deanna Taylor (DT), David Crabb (DC), Freda Sii (FS), Imran Masood (IM), and Peter Shah (PS). Ethical approval was gained by Lee Jones (LJ), help with recruitment came from FS, IM, and PS. Help with data analysis came from DT, FS, IM, and PS. The results were interpreted by LJ and reviewed, edited, and approved

by all authors. The work presented in this chapter has also been presented as a poster presentation at the Association for Research in Vision and Ophthalmology meeting (Honolulu, HA, USA, 2018); see list of supporting publications.

5.1 Introduction – Surgeon experience

All ophthalmologists will have patients under their care who have effectively only one seeing-eye. The fellow eye may have suffered severe loss of vision from various causes including trauma, surgical complications, and advanced disease (e.g. glaucoma), or may have had long-standing poor visual function from dense amblyopia. These patients who effectively have just one seeing-eye ('only-eye') are always a concern for their ophthalmologists, but particularly when the better seeing-eye develops problems that need surgical intervention, such as glaucomatous progression. However, in moving into a surgical zone, both patient and surgeon are faced with the hard fact that surgical complications in the intra - and post-operative period in an only eye may result in sudden, total, and permanent loss of vision, with life-changing consequences. It is for this reason that we believe that only-eye surgery is appropriately considered as 'high-stakes' surgery.

Complications encountered during or after surgery pose a real threat to patients' visual function, and loss of vision in the 'better' eye can have a significant impact on quality of life (Jones et al., 2017 (See chapter 2); Peters et al., 2015; Glen & Crabb, 2015; Kotecha et al., 2012; Ramulu et al., 2014). This is particularly true for only-eye patients where the 'worse' eye is significantly sight impaired. Incisional ocular surgery, such as trabeculectomy, generally carries a low complication incidence rate (Kirwan et al., 2013). Yet, potentially sight-threatening complications, such as postoperative infection and haemorrhage, cannot always be discounted, and unfortunately do occur following these routine procedures (Edmunds et al., 2002). Regrettably, such incidents have been reported in only-eye surgery (Eradurman et al., 2006), with a possible outcome of total extinction of the patients' residual vision. Thus, the decision to operate on a patient's only-eye is clearly not one that should be taken lightly.

Researchers have recognised the unique impact ophthalmic surgery can have on patients' psychological wellbeing (Cross et al., 2009; Janz et al., 2001). Indeed, only-eye patients have been found to be more fearful before surgery than binocular patients, citing blindness and surgical complications as their primary concerns (Marback et al 2012). Research has highlighted the increased levels of perceived stress amongst surgical staff when operating on complex or high-risk patients (Anton et al., 2015), and only-eye surgery often fits both these criteria. Therefore, we believe research into how ophthalmic surgeons approach only-eye surgery, such as strategies for risk reduction, and

management of performance anxieties inherent in this type of surgery, is warranted. The only-eye surgery-performing cohort of ophthalmologists in the hospital eye service can provide valuable insight into the realities of performing these high-stakes procedures, the challenges to overcome, potential strategies for effective coping, and service delivery issues. The purpose of this study was to explore ophthalmic surgeons' experiences of performing only-eye surgery with the aim to improve the journey for both the patient and the surgeon, and to minimise the risk to both.

5.2 Methods

In medicine stories of illness and healthcare experience are well recognised as a rich source of information. In qualitative research, stories told during interviews, help to set a patient-centred agenda. They may challenge what is already known, and can generate new insights and understanding. Thus, qualitative data can be an important educational resource to help in dealing with patients' problems holistically, and to enhance continuing professional development of health care staff. This type of research in ophthalmology has investigated patients' experience of visual impairment, and aspects of the patient journey (Cammack et al., 2016; Cross et al., 2009). This project is the first to focus on people who have vision in only one eye, and who have faced the challenge of having surgery on that eye.

This project uses extended semi-structured interviews, to learn more about what the experience of only-eye surgery is like. In particular, we want to find out how glaucoma patients and ophthalmic surgeons make sense of the only-eye experience for themselves. Qualitative methods, such as interviews, are believed to provide a 'deeper' understanding of social phenomena than would be obtained from purely quantitative methods, such as questionnaires (Silverman, 2000). Interviews are, therefore, most appropriate where little is already known about the study phenomenon, such as in the field of only eye surgery. They are also particularly appropriate for exploring sensitive topics the likes of surgical experience, as participants may not want to talk about such issues in a group environment such as focus groups.

Semi-structured interviews consist of several key questions that help to define the areas to be explored, but also allows the interviewer or interviewee to diverge in order to pursue an idea or response in more detail (Britten, 2006). This interview format is frequently used in healthcare-related research, as it provides participants with some guidance on what to talk about, which many find helpful. The flexibility of this approach, particularly compared to structured interviews, also allows for the discovery or elaboration of information that is important to participants but may not have previously been thought of as pertinent by the research team. A loose, semi-structured interview guide (See Appendix 1), with suitable prompts, was prepared that encourages participants to be expansive in their accounts, if required. However, the aim was to remain as flexible and non-directive as possible.

Sampling and recruitment: In qualitative research, the depth of the data is more important than the numbers in addressing the research questions (Frambach et al. 2013). A small number of information rich, in-depth interviews can have the same impact as many more, shorter interviews. Different sample sizes, depending on the qualitative approach, are cited from at least six for phenomenological studies, as with our study (i.e. a study of subjective experience), to approximately thirty-five for grounded theory research (Guest et al., 2006). A sample size of between five and twenty-five for phenomenological studies appears quite consistent within the literature (Creswell, 1998). As this study adopts an inductive approach, we do not seek generalisability based on large sample sizes, but rather the appropriateness and adequacy of the sample to yield a meaningful balance between thick data, and rich data (Tracy, 2010). Using these criteria, we decided to conduct individual interviews with ten ophthalmic surgeons (See Table 5.1). Purposive sampling was used whereby surgeons who were known to have experience of performing only-eye surgery were invited to participate. Research that is field oriented and not concerned with statistical generalizability often uses non-probabilistic samples. The most commonly used samples, particularly in applied research, are purposive (Miles & Huberman 1994). Purposive samples can be of different varieties, but the common element is that participants are selected according to pre-determined criteria relevant to a particular research objective.

An eye was considered an 'only eye' when significant loss of vision in this eye would be deemed life-changing with profound impact on the quality of life by both patient and surgeon. The vision in the fellow eye (usually the RNIB definition of severe sight impairment <3/60 or worse +/- end-stage visual field loss) was considered as insufficient to maintain the patient's current independent life-style and visual quality of life.

ID	Sex	Years performing only-eye surgery	Specialty	UK/Non UK based
P1	Male	>20	G; AS	UK
P2	Male	>10	G; AS	Non-UK
P3	Male	>10	G; AS	Non-UK
P4	Male	>10	G; AS	UK
P5	Male	>20	G; AS	Non-UK
P6	Male	<10	G; AS	UK
P7	Female	<10	G; AS	UK
P8	Female	>10	G; AS	UK
P9	Female	>10	G; AS	Non-UK
P10	Male	>10	G; P	UK

Key. G = glaucoma, AS = anterior segment, P = paediatric

Table 5.1: Participant characteristics

Data collection: The study was approved by the London – Chelsea Research Ethics Committee (Ref: 17/LO/1664) and conformed to the tenants of the Declaration of Helsinki; See Appendix 2. Consent from all participants was obtained prior to interview. Semi-structured face-to-face interviews were conducted by a university-based researcher (LJ). Two of the interviews were performed face-to-face via Skype. As per the guidelines by the World Health Organisation, an interview topic guide (See Appendix 1) was devised prior to commencing the study (Kajornboon, 2005). Details of the topic guide development are shown in Figure 5.1. Data collection took place between November 2017 and April 2018. Median (Interquartile range) interview duration was 35 (31-40) minutes. Completed, signed consent forms were kept securely as part of the Research Master File. Each participant was assigned an identifying number, which was used for all other research records in this study. A separate password protected file was kept on the Principal Investigator's computer detailing participants' names and their identifying numbers. This was the only link between participants' names and their identifying numbers. Field notes, recordings of interviews and interview transcripts were accessible

only to the research team using password protected computer systems. All equipment used for recording and paper filed notes were kept securely as part of the Research Master File. Once final dissemination is complete, all research data will be stored for 5 years as per University Hospital Birmingham NHS Trust guidelines.

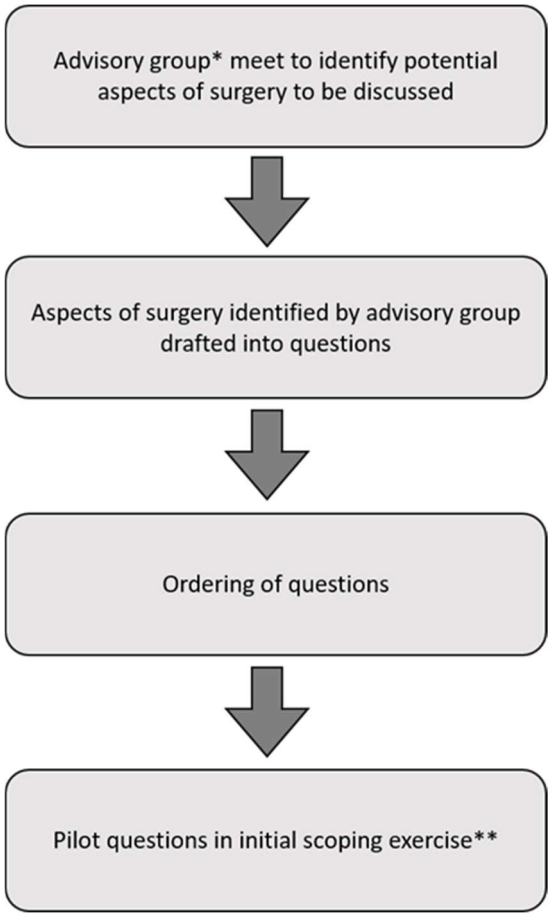

Figure 5.1: Process of interview topic guide formation. *Advisory group consisted of only-eye patients, consultant ophthalmologists, ophthalmologists-in-training, a psychologist and an ophthalmic research nurse, and established researchers in the field of ophthalmology. **Scoping exercise consisted of a preliminary pilot interview where suitability of interview questions was assessed.

Data management and analysis: The study was designed and reported following the guidance of the Consolidated Criteria for Reporting Qualitative Research (COREQ) for interview-based studies. All audio recorded interviews were transcribed verbatim via an online transcription service (www.sterlingtranscription.co.uk). All interviews were coded using both manual and computer-based methods (NVivo 11; Nvivo data analysis software). A thematic analysis approach was employed when analysing the data; this approach pays attention to common themes inductively identified and described across all of the participant narratives (Braun & Clarke, 2006). The focus is on identifying extracts in the interview transcripts that appear relevant in the terms of the research questions, which can be collected into categories across the data set. This is followed by the analysis at the broader level of themes, clustering different categories into potential overarching themes (Braun & Clarke, 2006). Two members of the research team (LJ and DT) independently interpreted all of the transcripts and developed preliminary codes based on impressions of recurring themes. Inter-rater reliability between the two coders was assessed by analysing a portion of the coded interview data (16% of total transcribed word count) using the kappa coefficient (κ). We established that the level of inter-rater reliability was more than acceptable between the two coders, $\kappa = 0.46$. There is debate in the literature regarding the sufficiency of the kappa statistic, however scores between 0.40 and 0.75 typically reflect fair to good agreement beyond chance. (Fleiss, 1981; Landis & Koch, 1977). Following individual data interpretation, the research team met to reflect on all of the interview data and discuss any differences of opinion regarding the coded themes. Once the research team were in agreement of the meaning of quotes and suitability of coding choices, a coding framework was created featuring all of the identified themes. Finally, collected codes were grouped based on the concepts of only-eye surgery they addressed, resulting in the identification of several emerging themes.

5.3 Results

Data were indexed according to the different areas of only-eye surgery that were discussed. As shown in figure 5.2, we identified four key emerging themes relating to (1) Material risk (2) Strategies for risk reduction (3) Training (4) Emotional impact. Direct quotes taken from the transcripts are italicised. These quotes were examples chosen to illustrate the key themes that emerged from the interviews. All included excerpts are annotated with a code given to the corresponding surgeon with a numeric to identify the order in which they were interviewed.

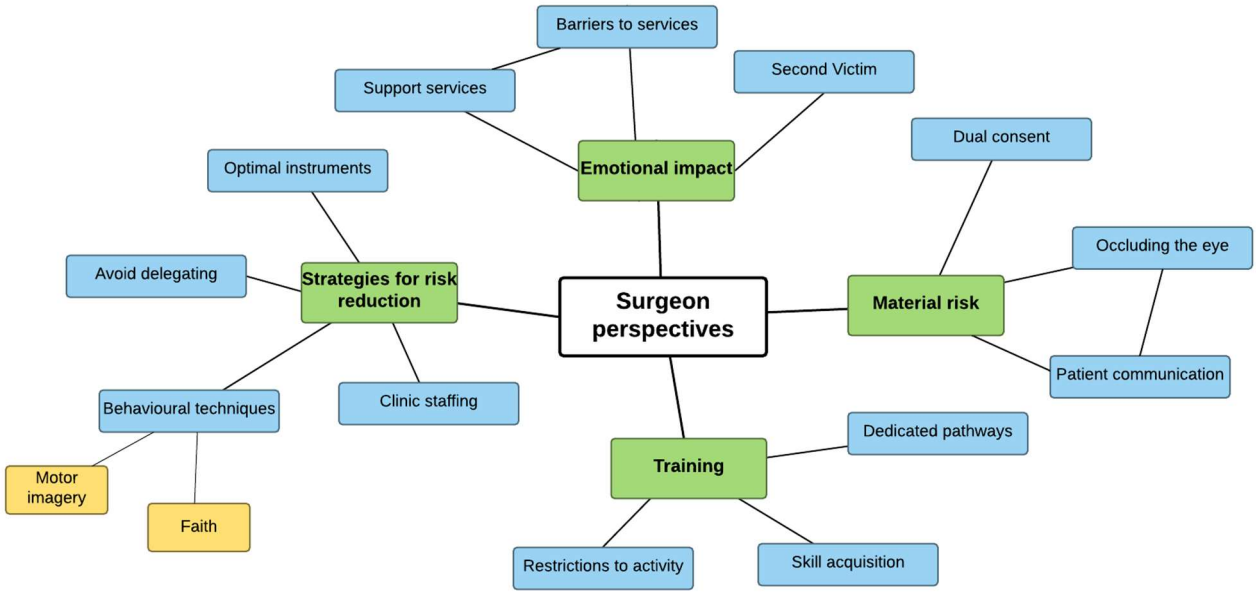

Figure 5.2: Diagram showing the main themes and subthemes that emerged from the surgeon analysis, and how different categories relate to each other.

(1) Material risk

A number of participants described concerns regarding the discussion of material risk during the consent process in only-eye surgery. There was an agreement that a conversation about the potential risks between the patient and physician is important. However, there were variances between the participants over how extensive such discussions ought to be.

The issue is you have to communicate what the material risk is. If the material risk is blindness, you have to communicate it. We have to articulate total extinction of vision, and I think that's absolutely right and very important. (P1)

I don't think it's necessary to dwell on it too much, but there needs to be a mutual understanding. I think it's kinder in a way to not solely talk about that point, it needs to be tempered with a sense of realism. (P7)

It should be an open discussion, which it most of the time is. There are patients who don't want to take part in that decision; they leave it entirely into your own hands. That's fair; that's good enough. (P5)

On occasion, the surgeons explained how they attempt to demonstrate the risks of only-eye surgery to the patient. To do this, some used methods to exemplify what the patient's life would be like if the surgery was not successful and the patient loses their vision. In addition, the surgeons supported the idea of family members being present when consenting only-eye surgery, to assist when deciding whether or not to go ahead with the procedure.

When we consent a patient for only-eye surgery, we insist they bring their relative, their nearest and dearest, and maybe their kids as well, and we patch them up for three hours in clinic and we sit them outside so they are totally blind. So they've been totally blind for three hours when we consent them. I strongly suggest to the patient that they bring their loved ones to the consultation, whoever's looking after them, and involve them in the decision. Because these are the people, if things go wrong, they're going to be looking after the patient for the rest of their life. (P1)

In other cases, the surgeons described how ensuring the patient is given a second or third opinion during the consent process, so that they are able to make an informed decision over whether to proceed with the surgery.

When you've got patients that are high-risk only-eye, it's always useful for the patient and surgeon if you've got two people doing the consent process. Certainly, joint clinics and multidisciplinary clinics allow for the opportunity for the patient to get a second or third opinion, so all are in agreement that they need this intervention. So, if something catastrophic does happen, and a patient goes blind, then at least they have that opinion from a number of people, not that it will be

any consolation, but at least the patient knows that a number of surgeons said the same thing, and I think that always helps. (P4)

(2) Strategies for risk reduction

Participants gave details about strategies they specifically integrate in only-eye surgery to help optimise outcomes. These were typically clinical in nature, such as ensuring optimal surgical instruments were available for the procedure, and that the most skilful clinic staff were assisting.

I don't want new nurses or scrub nurses or anybody else in my theatre at that time if it's an only-eye. (P9)

There was a general consensus there is often an aversion to delegating only-eye patients to clinic staff that are not of a suitable level of seniority.

The head of the department or the Medical Director would do all the only-eyes himself, just to take responsibility for it. (P3)

Participants identified behavioural techniques they adopt to prepare for only-eye surgery. Some participants adopted physical techniques such as motor imagery, whereby the surgical tasks are visualised and mentally performed prior to surgery, acting as a kinaesthetic opportunity to prepare for the procedure. Conversely, other surgeons relied on their faith and engaged in spiritual activity in order to help cope with the stresses of only-eye surgery.

I do mental preparation. I will visualise the steps that I will go through. I will visualise what may go wrong, and what I will do to undo that. I visualise even the routine, the basic steps. (P8)

With more complex cases, you go through in your mind the steps you are going to do. I've heard that Olympic divers do a very similar sort of thing. Before they even get up onto the podium they are going through their mind the exact number of turns and twists and whatever they have to do because it is over so quickly. It's got to be all pre-programmed in their head. (P2)

I've had some patients say to me, when I've asked them to sign a consent form for an only-eye operation, they say, well, we trust you, we have our faith in you, but we also have faith in God, okay, and we believe that God will get us through this.

In the same way, I have my faith as well. So, before I operate, I always pray. I take on some very difficult and crazy cases where sometimes I'll be doing a lot of this surgery for the first time in my life, but I do it because I also have faith, and I pray, and I believe God helps me. (P4)

One suggestion for reducing risk intra-operatively was to ensure only eye patients were operated on by teams of highly experienced surgeons, rather than a single surgeon.

> ***There's been instances where another surgeon being there has made a crucial difference to the outcome, because they've spotted things that I may not have spotted because I was busy with something else. (P4)***

Yet, the consensus was that only eye patients are often operated on by just one surgeon.

> ***It's a good idea to do difficult cases together, but because our outcomes are usually not lethal, it's not about life or death, we can't finance a second surgeon. (P3)***
>
> ***In many branches of surgery, high-risk cases where the impact of failure is massive, are done by two surgeons, or teams of surgeons. In ophthalmology often there's just one surgeon. I wonder if we are missing something just because it's a small organ. (P1)***

Participants also expressed preference for avoiding this approach, and warned of potential hazards of high-stakes procedures being performed by teams.

(3) Training

The participants correlated a lack of surgical experience for ophthalmologists-in-training with concerns about the future provision of care for only-eye patients. For example, senior surgeons expressed doubt that the current training programme in ophthalmology would provide sufficient exposure to high-stakes procedures, such as only-eye patients. An explanation for the dearth in experience was the increased time restrictions on surgical activity for ophthalmologists-in-training.

The trainees are not getting the training. The number of cases are dropping, they are shortening the number of training years, so you [trainees] are actually being compressed in both ways. (P8)

Participants reported their concerns that insufficient training and exposure to only-eye patients will ultimately impact on new ophthalmic surgeons' ability to manage these cases upon reaching consultancy level.

I would say, looking at the last five years, I can't think of a single trainee who I would feel had the necessary technical ability, bravery, and surgical resilience to be safely allowed to do these cases. I just wonder what's going to happen when they become young consultants. I just don't think they will have the necessary skill set. (P1)

They will become a consultant with probably less than 50% [experience] as the previous generation, so that will be a problem. (P8)

One of the things that generally is consultant only is only-eye [surgery]. I think we try to protect our trainees as much as possible. But there has to be a tipping point where they're going to have to deal with it at some stage. (P2)

What you do not want is get to the end of your training, become a consultant, and then all of a sudden be tasked to operate on one of those [only-eye] cases. (P7)

Participants acknowledged that more needs to be done in order to prepare ophthalmologists-in-training for operating on only-eye patients. There were recommendations on how to overcome the issue of insufficient experience, such as the advent of specialised training programmes for only-eye care, allowing for exposure to these patients whilst under close supervision.

I think it's important that we identify the best people, and then they are given focused training, focused mentoring by senior surgeons who do that kind of surgery, and gradually get them to that level. I think that's what we need. In this kind of surgery, you've got to get the people who are the best, because patients only have one chance. This is what we call one-shot surgery. If we get it wrong, the patient's blind for the rest of their life. (P4)

(4) Emotional impact

Participants in this study recognised only-eye surgery as high-stakes surgery, carrying potential for devastating adverse events. Amongst our cohort, a number of surgeons had experienced losing an only-eye, resulting in catastrophic loss of vision for the patient. Often in these cases, the surgeons described being burdened with a sense of personal

responsibility for their patient, and expressed how they are then required to shoulder the blame for losing the eye for the patient. These participants provided insight into the strong negative reactions they experienced following such incidents.

We lost a true only-eye, he went blind. Well it doesn't leave you, I still feel like I could have done something different. I feel like if the time was slightly different, if we weren't so stressed, if we weren't so under pressure, I think we would have said there's something not quite right. I still feel partly responsible for him. (P8)

For participants who had not yet experienced losing an only-eye, they expressed concern over how this would impact on their career and the psychological sequelae of such an event.

I'm lucky not to have had an only-eye disaster, yet. I'll probably remember that for the rest of my life, when that happens, which it probably will. (P10)

The participants advocated the need for formal mechanisms to support surgeons after losing an only-eye, to help develop strategies to cope with negative surgical outcomes.

I think there needs to be a better support mechanism. I think, if someone has lost an only-eye and they're very distraught by it, they need a mentor to talk to, someone who has lost an only-eye. So, you need – a bit like the self-help groups, where you have psychological therapy. (P4)

Yet, the participants noted that there are a lack of formal pathways to find professional support services in the event of losing an only-eye. Participants also noted perceived barriers when it came to seeking out such services.

There's no guidance on how surgeons can seek out help for themselves when incidents like this happen. (P8)

I think we're very busy. We don't have time to do that [seek support services]. Something else would have to give. (P6)

5.4 Discussion

Only-eye surgery can be challenging for the ophthalmic care team. In medicine, stories of healthcare experiences can provide a rich source of information to help generate new insights. However, qualitative research is frequently under-represented in ophthalmology (Jones & Jefferis, 2017), and yet has the potential to offer significant contributions to knowledge and understanding of eye care. We sought to explore ophthalmic surgeons' experiences of performing high-stakes procedures on patients with only one seeing-eye.

Discussion of risk is of paramount importance in only-eye surgery. Our findings highlight differences in how surgeons disclose material risks in only eye surgery. Participants stressed importance of patients' understanding of risks of surgery, regardless of how unlikely adverse outcomes may be. Yet, other participants voiced concerns over a heavy focus on risks of vision loss, as surgery is generally successful. This discordance is pertinent given the landmark change in the position of the Supreme Court regarding informed consent (Edozien, 2015). Until recently, the UK Supreme Court followed the principles of the Bolam Test. Such principles state that, in the event of surgical complications, a surgeon would not be deemed negligent if they had acted the same way other competent surgeons would have (Newman, 2016). However, this paternalistic approach to medicine is no longer tolerated, as demonstrated by the introduction of the Modified Montgomery Test (Sokol, 2015). This standard of care obliges surgeons to provide sufficient information to patients, including disclosure of risks of proposed treatment. In medicine, there is concern over the use of a 'one-size-fits-all' approach applied to heterogeneous populations (NCEPOD, 2010). For example, greater material risk should be attached to surgery on an only eye, as opposed to the same surgery on a patient with good bilateral vision. Yet, participants expressed aversion to appearing pessimistic when discussing surgical risks, a belief in contrast to the principles of the Modified Montgomery Test. Methods of demonstrating risks of only eye surgery included occlusion of the only eye. Our results indicate variances between surgeons regarding discussion of material risks in only eye surgery, suggesting the principles of the Modified Montgomery Test are yet to be fully recognised in this area of ophthalmology.

Our study has interesting findings regarding how only-eye surgery is approached by ophthalmic surgeons. Indeed, a career in surgery not only requires extensive medical knowledge, critical thinking skills, and sharp motor control, but also endurance and stamina, both physical and psychological. Surgeons must be able to maintain attention,

make split-second decisions, and retain fine motor control throughout the entirety of a surgical procedure, sometimes lasting several hours. The complexities, implications, and risks associated with operations create a generally stressful environment (Arora et al., 2010; Maher et al., 2013). Furthermore, advances in surgery continue to increase the demands on surgeons. It was acknowledged that only-eye procedures can evoke elevated levels of stress for the surgical team. Indeed, self-reported anxiety is higher when the procedure is considered high-stakes (Anton et al., 2015).

There is a need to develop methods to reduce stress in the operating room, and also to maximise skill acquisition and retention in learning or simulated environments. Mental skills are psychological strategies used to help performers reliably achieve their ideal mental state for performance (Williams, 2010), and may be able to help surgical trainees, and even experienced senior surgeons, to reduce stress and enhance their learned skills in the operating room. Examples of mental skills exercises might include mental imagery; goal setting; energy management, i.e. relaxation strategies; and attention management. Mental skills training curricula have been shown to be effective at enhancing the performance of several groups who have to perform under high stress conditions such as military pilots during training exercises (McCrory et al., 2012), The United States Navy, Sea, Air, and Land teams during underwater demolition training (Selder et al., 1989), and amongst police special forces (Le Scanff & Taugis, 2002). In particular, over the past two decades, a variety of intervention techniques have been prompted to help athletes develop mental skills to enhance their performance in such sports as tennis (Daw & Burton, 1994) and swimming (Sheard & Golby, 2006). The success of such interventions has seen an increase in mental skills preparations being implemented amongst elite athletes in sports including rugby (Rowley et al., 2012), cricket (Jooste et al., 2013), and skiing (von Guenthner et al., 2010). This overlap between sport psychology and surgery is perhaps not surprising, as both require an element of goal setting and strong motivational benefits. However, many sports follow a 'zero-sum' game structure, whereby the total number of wins and losses adds up to zero, and thus one party benefits at the direct expense of another party (i.e tennis, chess, etc.). In contrast, the process of a surgical intervention can be much more likened to a 'positive-sum' game, where the strategic approach attempts to satisfy the desires and needs of all concerned (i.e. the patient, the surgeon, the patient's family). For this reason, the stress applied to the

surgeon responsible for securing a successful result will inherently be larger, as in the event of an unsuccessful outcome, the losing party will far outweigh the winning party.

Participants in this study reported a number of mental skills used to help optimise performance in these stressful procedures, including motor imagery. The use of mental skills and mindfulness have previously been shown to potentially reduce stress and improve performance (Stefanidis et al., 2017; Fernando et al., 2014). Moreover, evidence indicates that surgeons who undertake mental skills training have better outcomes on measures of anxiety (Stefanidis et al., 2017). Our results identify coping strategies used by surgeons before only eye surgery to optimise performance during stressful situations.

Our findings introduced the concept of only eye surgery being performed by two or more surgeons. This intra-operative strategy for risk reduction was described as an opportunity for another expert to critique the procedure, in an attempt to ensure nothing is missed. However, some participants perceived this approach to be counter-productive, suggesting team procedures can lead to adoption of more risk-averse or overly foolhardy behaviours. The advocacy for only eye procedures performed by two or more surgeons echoes how exceptional cases are managed in other fields of medicine, such as cardiothoracic surgery. In this specialty, implementation of a Star Chamber, whereby surgeons refer complex or high-stakes patients to the Star Chamber who assess what the patient should be offered, has been used in an attempt to improve surgical outcomes (Nashef, 2017). If the Star Chamber recommend surgery, it is a requirement that the procedure is performed by a minimum of two consultants. Other disciplines in the UK are considering implementation of a Star Chamber (ACGBI, 2016), however there appears to be no such movement in ophthalmology. Yet, such initiatives as the Star Chamber may help to minimise intra-operative risks during only eye surgery.

Participants described how medical training in the UK has experienced dramatic reform, and expressed concerns over how this may affect standards of care in ophthalmology. Changes in educational theory (Reznick & MacRae, 2006), and the European Working Time Directive (Department of Health, 2009) have limited training opportunities for ophthalmologists-in-training. As a result, procedures such as trabeculectomy feature less often in trainees' timetabled clinical activity (Rodrigues et al., 2013). Work-hour restrictions and a demise of the 'mentor' model in medical training may have damaging consequences for acquisition of technical skills and surgical

resilience (Cope et al., 2017). Indeed, consultant surgeons have reported concerns over capabilities of the newer generation of trainees and how this may impact patient care (Rashid et al., 2012). Although progress in technology has led to the advent of valuable training opportunities, such as 'wet-lab' simulations (Lee et al., 2006), such environments are unable to mimic the true reality of operating on a patient's only eye. Participants stressed the essentiality of combatting these training barriers, and gave suggestions for purpose-designed training programmes for complex procedures. Such programmes may enable appropriate access to high-stakes patients and nurture the learning processes for ophthalmologists-in-training. This finding spotlights concerns with surgical training in ophthalmology, a problem first identified almost two decades ago (Gibson et al., 2002). If this trend continues, there may be necessity for specific training fellowships to gain clinical competency, and we propose that only eye training must not be overlooked.

Another emerging theme was the importance of mentoring in only eye surgery. Participants described how a good mentor has helped them to become an effective only eye surgeon. Typically, a mentor will be a senior member in the field who guides a trainee professionally and personally by facilitating learning through observation and modelling (Cope et al., 2017). There is concern that mentoring has become a lost art in medicine (Rohrich, 2003), and participants in our study explained that a mentor can offer significant support when caring for only eye patients, and formal recognition of mentoring may be needed. In line with previous research, our results highlight barriers to mentorship as a lack of formal recognition of the role, resulting in time commitment issues and a scarcity of appropriate mentors (Entezami et al., 2012). Fostering of strong relationships between mentor and trainee could play a crucial role in alleviating concerns raised in this study about training in ophthalmology and only eye surgery.

A number of participants in our study had experience of losing an only-eye, resulting in total extinction of vision for the patient, and usually a life of full-time dependency on others. Participants described their responses to these incidents and how the psychological sequelae has impacted their career as a result. A recurring sense of personal responsibility and blame was reported, and participants frequently remarked on the lack of formal and professional support for physicians when unpredicted outcomes occur. In medicine, the term 'Second Victim' was coined to recognise that, in addition to the crucial needs of the patient and their families when such events occur, the surgical team may also suffer in these devastating instances (Wu, 2000). Participants reported a

sense of fear at the thought of unfavourable results in only-eye surgery, and described their concern over a perceived lack of avenues to seek professional support in the event of such incidents. This finding is particularly noteworthy as the Royal College of Physicians has recently outlined ten areas for urgent action to obviate a crisis regarding the mental health of surgeons in the UK (Royal College of Physicians, 2015). Research estimates that almost 90% of physicians perceive a lack of available time to access support services when coping with Second Victim experiences (Hu et al., 2012). Growing attention is now being placed on the mental wellbeing of surgeons in the UK (Gerada, 2017), and the importance of such support services as the Practitioner Health Programme is being realised (Brooks et al., 2011). However, it remains that only 57% of NHS trusts have a policy to support staff mental health (Sloan et al., 2014). Participants in our study perceived a lack of options for support for surgical staff in the event of poor outcomes in only-eye surgery, reflecting the dearth in recognition and understanding of the Second Victim phenomenon in the field of ophthalmology.

The strengths of this study are that it is the first of its kind in ophthalmic surgery. By adopting a qualitative approach to this subject, a number of important themes have emerged which have provided an excellent basis for further work. The study is limited in that a small number of surgeons were interviewed and the surgeons in question were all experienced glaucoma surgeons. This may however be due to the nature of glaucoma in that there may be a greater proportion of patients who are only-eyed particularly in complex glaucoma practices. Furthermore it is important the future studies consider the views of less experienced surgeons.

The implications of losing an only-eye are massive for both the patient and surgeon. This study clearly identifies important themes that are of great relevance to surgeons who regularly perform only-eye surgery. These include risk management, training, and emotional factors. Further work in needed in each of these areas to clearly define best practice to enable a safe and seamless patient journey.

5.5 Introduction – Patient experience

It is often stressed that a diagnosis of glaucoma does not necessarily mean the patient will ultimately experience a total extinction of vision (Green et al., 2002; Crabb, 2016). Rather, estimates suggest that around 1 in 20 treated patients are at risk of serious visual impairment due to glaucoma (Saunders et al., 2014). Whilst these figures are likely to be somewhat comforting for the majority of those diagnosed with the disease, it remains true that a small number of patients will experience significant visual disability as a result of their glaucomatous vision loss. Furthermore, glaucoma has a progressive impact on patients' daily activities and quality of life, whereby more advanced disease incurs more pronounced difficulties (Ramulu, 2009; Peters et al., 2015; Jones et al., 2017 [See chapter two]). As such, patients living with advanced-stage glaucoma will likely face exceptional challenges in their day-to-day lives compared to individuals with healthy vision, and even those living with mild or moderate glaucoma.

In addition to the threat of visual disability, patients may need to undergo surgery to treat their glaucoma. When glaucoma cannot be controlled medically, surgical intervention may be required. Trabeculectomy is the most commonly performed surgical intervention in glaucoma and is generally successful at reducing IOP (Gedde et al., 2012), even in complex, high-risk populations (Shah et al., 2012). Advancements in education and technology have reduced the likelihood of complications after surgery (Kirwan et al., 2013). However, the procedure remains associated with potential risks such as hypotony, or in more extreme cases, endophthalmitis (Edmunds et al., 2002). Furthermore, the longevity of trabeculectomy is difficult to predict (Landers et al., 2012) and factors such as race and age can affect surgery success rates (Broadway & Chang, 2001).

Researchers have recognised the unique impact ophthalmic surgery can have on patients' psychological wellbeing (Nijkamp et al., 2004; Marback et al., 2007). However, there has been limited investigation into the experiences of 'only-eye' patients undergoing ocular surgery. In this instance, 'only-eye' refers to an eye where significant loss of vision would have a profound impact on patients' quality of life and would likely result in meet the criteria for severe sight impairment. Glaucoma only-eye surgical patients are those who require surgical intervention on the better-seeing eye in an attempt to slow glaucoma progression. The glaucoma only-eye population are among those who are at risk of significant visual impairment, are likely to be living with severe visual disability, and face the daunting reality of undergoing surgery on their only-eye.

As such, research into the experiences of this cohort of advanced-glaucoma patients is warranted. The aim of this study is to learn more about the realities of only-eye surgery from the patients' perspective, before, during, and after surgery. In particular, we were interested in learning how patients cope when undergoing these high-stakes surgeries and what can be done to improve the surgical journey for only-eye patients.

5.6 Methods

Individuals who met our criteria for only-eye patient were invited to participate in an interview. As discussed in Section 5.2, an eye was considered an 'only eye' when significant loss of vision in this eye would be deemed life-changing with profound impact on the quality of life. The vision in the fellow eye (usually <3/60 or worse +/- end-stage visual field loss) was considered as insufficient to maintain the patient's current independent life-style and visual quality of life.

Participants were required to have undergone glaucoma surgical intervention on their only-eye. There was no specification for amount of time since operation. Furthermore, participants were required to have the ability to communicate in English and provide informed consent. Details of patient characteristics and surgical history are shown in Table 5.2. The study was approved by the London – Chelsea Research Ethics Committee (Ref: 17/LO/1664) and conformed to the tenants of the Declaration of Helsinki; See Appendix 2. Consent from all participants was obtained prior to interview. Participant information was anonymised before being entered into a secure computer database.

Semi-structured interviews were conducted between December 2017 and April 2018. Interviews were audio-recorded with the permission from the participant. As discussed earlier in this chapter (See section 5.2), an interview topic guide was created prior to data collection. Interview questions were open ended and asked in such a way that required minimal interviewer input and encouraged detailed responses from participants. Care was taken not to ask leading questions, although prompts were occasionally used to encourage participants to expand on their responses. It was emphasised prior to the interview that there were no right or wrong answers and that participants would be given the opportunity to expand or clarify any points at the end of the interview.

Interviews were conducted face-to-face by a male university-based health psychology researcher (LJ). The majority of interviews were conducted with only the participant and researcher present, but a small number of participants chose to have a friend or family member present in the room. The study followed the COREQ. Audio files were transcribed and analysed. As per the data analysis described in section 5.2, a

thematic analysis approach was adopted. Similarly, transcripts were read and re-read, themes were identified, and example quotes were chosen to illustrate these themes

Code	Age	Sex	Ethnicity	Diagnosis	Most recent only-eye procedure
G1	66	Male	Caucasian	POAG	Phacoemulsification
G2	58	Female	Caucasian	SOAG	Baerveldt Tube
G3	54	Female	Caucasian	PCG	Trabeculectomy
G4	59	Male	Caucasian	JOAG	Trabeculectomy
G5	66	Male	Afro Caribbean	POAG/SACG	Trabeculectomy
G6	61	Male	Caucasian	JOAG	Trabeculectomy
G7	74	Male	Indian Asian	POAG	Phacoemulsification
G8	73	Female	Caucasian	POAG	Trabeculectomy
G9	32	Female	Bangladeshi	JOAG	Trabeculectomy
G10	29	Male	Indian Asian	SACG	Trabeculectomy
G11	49	Male	Caucasian	SACG	Baerveldt Tube

Key. POAG = primary open angle glaucoma, SOAG = secondary open angle glaucoma, PCG = primary congenital glaucoma, JOAG = juvenile open angle glaucoma, SACG = secondary angle closure glaucoma

Table 5.2: Participant characteristics

5.7 Results

Data were indexed according to the different areas of only-eye surgery that were discussed. Figure 5.3 shows the three key themes that were identified; (1) emotional impact of only-eye surgery; (2) coping with only-eye surgery; (3) improving the patient surgical journey. Direct quotes taken from the transcripts are italicised. These quotes were examples chosen to illustrate the key themes that emerged from the interviews. All included quotes are annotated with a code given to the corresponding participant.

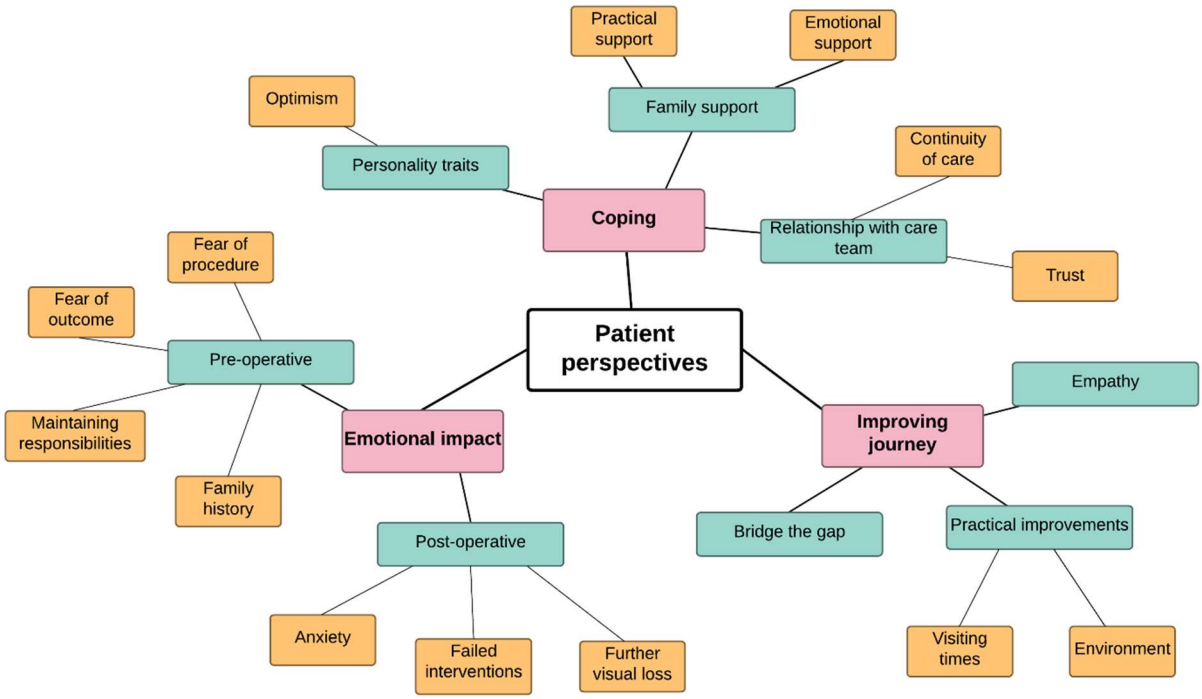

Figure 5.3: Diagram showing the main themes and subthemes that emerged from the patient analysis, and how different categories relate to each other.

(1) Emotional impact of only-eye surgery

Participants described their strong negative emotional response to learning they must undergo surgery on their only-seeing eye. A common theme across the patient narratives was an overwhelming sense of fear:

> ***I walked out of there and I was absolutely devastated, completely and utterly devastated. The whole world came crushing down around my shoulders, I went downhill very, very quickly. If you looked at it today you'd***

probably say I was majorly depressed, I didn't know how to get out of it. (G2)

Along with the initial distress of learning of the necessity of only-eye surgery, a number of participants reported a sense of fear regarding the potential outcomes of surgery:

Nothing in life is guaranteed and you do put your life in the surgeon's hands really. When I met my surgeon it was - I've got to be honest, I was terrified because I just had no idea where I was going and what was going to happen. (G6)

I think more than anything it's the worry that if something goes wrong you've got nothing. (G4)

When you're at the first stages it's very scary because you don't know what's going on. (G11)

The fear of potentially negative outcomes of surgery was particularly pronounced in patients who had a responsibility for others, where they had concerns as to how they would be able to continue in their care giving role:

It was a horrendous time, absolutely horrendous time. My experiences of going into an operation with a one and only eye, one word to describe it is absolutely petrifying. You don't know what's going to happen. That was very daunting because I'd got a very young little girl, and didn't know what was going to happen when I came out of it. (G2)

In some cases, participants had witnessed a family member losing their vision to glaucoma, and this close involvement made them particularly fearful for themselves:

My brother has got the same condition but he's gone blind, so that was a worrying factor for myself. (G3)

Indeed, the thought of undergoing only-eye surgery was worrisome for many participants. Yet, a number of participants reported that the most concerning aspect of their surgical journey was the post-operative period, where there was significant anxiety immediately after surgery about the surgical outcomes:

I think the scariest bit was when you come out of surgery, where you come out of the theatre and you've got an eyepatch and it's scary. It was scary and

you think what am I going to see when I get this taken off - will I be able to see when they take the eye patch off. (G8)

Sometimes I wake up crying. I just feel very scared during the night [after surgery] and I don't have anyone to say to that I'm scared. (G9)

When I had my second surgery when I first woke up I couldn't see straightaway and I panicked like Hell. Although your surgeon has told you that everything has gone fine, everything is well, you're still lying there thinking, okay, I'll find out tomorrow morning when these bandages come off. I think that's where I've probably felt the most isolated, over that night. (G2)

Immediately after the operation and during that first night, you don't know, and the next morning they take off the eye patch and that was a relief because on all occasions I could still see. But between the operation and taking that eye patch off, pure panic. (G8)

I lay in bed for six weeks, I couldn't see the light above me and if I'd had a gun I'd have put a bullet in my head. I used to sit up and break my heart. (G11)

Many of the participants in this study had undergone a substantial number of surgical interventions. A common consensus was that 'failed' surgery, i.e. where IOP was no longer stabilised, was a particularly emotional event. One participant described their feeling of desperation and the hope that more could be done to save their vision:

It started to reject. I panicked, really, really panicked. It was a tough time, it really really was. My surgeon said to me - I can't promise you anything but we'll give anything a go. At that point I was like just try anything; just do anything, anything you can do. (G2)

The fear of being unable to cope with further visual loss was a common worry for participants, with concern being expressed as to how they would be able to continue life with very limited residual vision. This was a particularly concerning aspect:

I'll be honest with you, I said to the wife, I said if I'd lost my sight you would have found me in the road [deceased]. Because I'm not the sort of person,

I just couldn't - I meet people who have been remarkable by coping with it. I quite frankly just don't think I could. (G6)

(2) Coping with only-eye surgery

There was an array of coping mechanisms described by the study participants regarding what helped them to understand and come to terms with only-eye surgery. Participants frequently expressed that building a good relationship with their care team facilitated a sense of trust which helped them to cope with the anxieties relating to surgery. The responses highlighted the importance that is placed on continuity of care in these high-stakes surgeries:

I feel safe with the physician, but that's only because the doctor, the surgeon, I've got a relationship with them. I've got his number on my phone, he's been there for me but I think the journey leading up to that is the scariest part. (G11)

My doctor, I say that he is a gift from God. He knows how to speak to the patient and that's the main thing. (G7)

I think a lot of it has got to do with the confidence that your surgical team give you. The more they discuss with you and what may happen, what your thoughts are about it, what they're going to attempt to do. To me, going in there knowing that it could go the wrong way as well as the fact that it could come out the right way is a very big thing. (G2)

Other coping mechanisms came from family support in both emotional and practical ways. Emotional support from family and friends in negative times, as well as practical support, such as when instilling eye drops, were both considered by participants to be of vital importance to their wellbeing:

I was extremely fortunate that I've got a very good family around me. It is devastating and you need the support of your family. (G2)

Coping with only-eye surgery was often helped by developing positive personality traits, such as having an optimistic attitude towards surgery. Participants described how they would attempt to maintain a positive outlook in order to reduce their concerns about glaucoma:

To come out of surgery with anything at all is better than what the future held for me anyway. I think excited is another word, because you are excited at what's going to happen. (G2)

I wasn't fearful because I was confident that whatever happened, I had made the right decision. (G1)

(3) Improving the patient's surgical journey

The participants in this study described the immense impact glaucoma has had on their lives and the difficult challenges they have faced, including significant loss of vision and multiple surgical procedures. Many of the participants explained the situations which they found to be particularly traumatic, and provided some suggestions as to what could be done to improve patients' experiences of only-eye surgery.

In some cases, participants described how their healthcare professional lacked empathy when delivering the diagnosis of glaucoma and discussing the management of the disease:

It was a very cold, callous response and it was jolly insulting. As it got worse they said you're beyond what we can do here. If we don't refer you to somewhere else you'll lose your sight forever. (G6)

Some participants felt that their healthcare provider was notably bleak when discussing the progression of their glaucoma, describing how they were informed nothing could be done to protect them from this disease:

The consultant sat there and he said I'm really sorry, there's nothing I can do for you sweetheart. He said that's what the glaucoma does to you. I remember my husband saying is there absolutely nothing that you can do. He said no I'm sorry. He said you're going to go blind and that's it. (G2)

It was suggested that healthcare providers must do more in order to bridge the intellectual gap between themselves and their only-eye patients to ensure that treatment regiments are patient-centred and help them to understand their diagnosis:

Surgeons have somehow got to try and bridge the intellectual gap to become empathetic towards the patients as well, especially in one eye surgery. (G6)

Moreover, participants described the importance of a more personal and humanised approach to only-eye surgery:

Yeah so it's being made to feel you're a person, not a number on the list. (G8)

There were also practical suggestions on how to make the only-eye surgical experience less daunting for the patient. Examples included music to help soothe the patient and relieve anxiety, as well as allowing relatives and caregivers to remain with patients while preparing to undergo surgery:

I'm very nervous, really. I like to maybe have some entertainment, in my perception anyway. Like having a bit of nice music in the background. (G9)

My husband was allowed to stay with me until I actually went - not into theatre, but just outside it. He came with me as they were taking me down there. I know that's not always possible because of things that happen. I think it's just people talking to you and telling you what's going to happen, isn't it? Making you feel safe and comfortable. (G2)

5.8 Discussion

To our knowledge, this is the first study to investigate only-eye patients' experiences of undergoing glaucoma surgery on their better-seeing eye. Surgery is a major trauma and is associated with significant patient anxiety (Munafò & Stevenson, 2001). In ophthalmology, patients have a tendency to show high levels of anxiety during the pre and postoperative periods, as well as during surgery (Marback et al., 2007). Reasons for ocular surgical anxiety are multifactorial, for example, anxiety may be the result of a lack of information about the procedure, expectations of results, and previous negative surgical experiences (Nijkamp et al., 2002; Nijkamp et al., 2004). Many of the participants in this study had undergone a number of glaucoma surgeries and reported aspects of visual disability as a consequence of their glaucoma. Indeed, participants reported feelings of fear and distress when told of the requirement of surgery on their only-eye. A number of participants expressed that their fear was at its most intense after surgery, whilst the eye was bandaged and occluded, thus not knowing the outcome of the procedure. This finding is in line with previous evidence that self-reported anxiety is high on the day after surgery for cataract patients due to concerns over what to expect from surgery (Nijkamp et al., 2002). This finding emphasises the high importance of postoperative counselling by patients' healthcare teams to ensure the patient is given adequate information on how the surgery went. This is especially important for only-eye patients where negative surgical outcomes might incur significant visual disability. In addition, previous research highlights that self-reported postoperative anxiety is higher when the individual has already undergone a previous ocular surgery (Foggitt, 2001; Nijkamp et al., 2004). This factor is important to consider for only-eye surgery as, at least in this study, many only-eye patients are likely to have undergone previous ocular surgeries given their advanced disease state, and therefore it may be beneficial to introduce extra precautions to help reduce postoperative anxiety.

Participants in this study described a number of coping mechanisms used to help manage their anxieties relating to only-eye surgery. Typically, participants described their reliance on supportive family members and friends, or developing positive personality traits to help cope with glaucoma surgery. Effective coping is an important component of good wellbeing and quality of life. Patients living with chronic illness who are able to cope with their disease are more likely to report improved subjective health, less distress, less fatigue, and more energy (Lorig et al., 1999; Lorig et al., 2003). Previous evidence has

found that glaucoma patients often adopt specific behaviours and techniques to help adapt to their glaucomatous vision loss (Glen & Crabb, 2015). Our findings shed light onto how glaucoma patients cope when undergoing high-stakes surgical procedures. Knowledge of coping strategies are important when understanding the surgical journey of glaucoma patients, and may ultimately help to provide better insight into the impact of glaucoma and help to inform patients, as well as professionals specialising in eye-care, about potential management strategies and coping behaviours relevant to glaucoma surgery.

Participants advised that more needs to be done to improve the surgical journey for only-eye patients in the hospital eye service. There were a number of suggestions on how this could be done, such as greater support from the care team, reduced separation from family, and specific environmental changes. For many participants, a key factor was the need to feel supported by their surgeon and care team. Previous literature has shown that a supportive care team who are able to comfort patients and help them to understand their diagnosis is fundamental to fostering a trusting relationship between patient and surgeon (Cross et al., 2009). Our findings echoed these sentiments, where participants expressed feeling safe in their surgeon's hands, and that they would be confident that the care team would be able to help if surgery did not go to plan. In the current climate this may be a particular challenge as surgical rotations can often be geographically diverse, where surgeons may be required to move from institution to institution, undermining the ability to build significant relationships and provide continuity of care to patients. Yet, as our findings demonstrate, continuity of care appears to play an important role for patient wellbeing. While many of the study sample reported a good relationship with their healthcare professionals, a number of participants reported negative experiences, such as a lack of empathy or a dogmatic attitude when discussing surgery. Participants described how these behaviours displayed by their care team led them to develop a fatalistic attitude, believing that nothing could be done to save their vision and that they would experience blindness as an ultimate result. Evidence indicates that such attitudes may result in patients delaying or avoiding surgery (Temporini et al., 2002), which could result in further visual loss. As such, it is imperative for the surgical care team to be aware of the importance of the patient-surgeon relationship, including partnership, trust, and confidence, particularly when patients are at risk of significant disability as a result of delayed surgery.

In addition to forging supportive patient-surgeon relationships, participants described some practical elements to only-eye surgery which may improve the surgical experience. The use of music at various stages in the surgical process was desired by some participants. Yet, evidence suggests that music may have no influence on patients' surgical anxiety (Allen et al., 2001). It is advisable that this be discussed between the patient and their care team on an individual basis. Participants also reported that hospitalisation due to surgery results in separation from their supportive others, which further compounded their feelings of anxiety and distress. One solution was to allow extended visiting hours for only-eye patients and allowing supportive others to be present when preparing for surgery.

To conclude, surgical intervention on an only-eye is a significant event for patients living with glaucoma. Learning about the necessity of surgery, and concerns of the outcome post-operatively represent particularly worrisome periods for only-eye patients. However, a number of coping mechanisms may be employed to help manage the anxieties of only-eye surgery, and improvements in healthcare delivery for only-eye patients are available. The findings of this study may be used to help inform patients, their carers, and those working in the hospital eye services about the realities of only-eye surgery, the challenges to overcome, and potential strategies for effective coping and service delivery.

Chapter Six – Summary of main findings and future work

6.1 Overview of findings

The aim of this work was to investigate aspects of the patient journey in glaucoma using a reductionist approach, focusing on the early and late stages of the disease. The work supports the large body of literature evidencing the negative effect of glaucoma on patients' quality of life. Specifically, this work emphasises that glaucoma can impair patients' vision-related quality of life even in the early stage of the disease, as well as having a more profound effect later in the disease. Both quantitative and qualitative methods were used when addressing the research questions and add to the existing knowledge of the patient journey in glaucoma. This thesis identified and addressed prominent gaps in the literature surrounding the impact of glaucoma and these are summarised here:

The study reported in **Chapter 2** evaluated the relationship between vision-related quality of life and visual field loss in people from glaucoma clinics. Trends in responses on the NEI VFQ-25 were assessed against better-eye MD using a linear regression model and a spline-fitting method that can highlight where a monotonic relationship may have different stages. The analysis highlighted that on average a patient loses approximately 2 units (out of 100) on the NEI VFQ-25 for every loss of 1 dB better-eye MD, up to approximately -5dB. Deterioration then appears to slow before a more rapid phase of change of around 4-5 units per 1dB loss after better-eye MD worsens beyond -15dB. The results of this study support the concept of a visual field threshold for severe functional impairment in glaucoma and challenges evidence which indicates a linear decline in vision-related quality of life and worsening MD.

In **Chapter 3**, responses on general health and disease-specific PROMs were assessed for group differences between trial arms for patients in the UKGTS. The average percentage change on PROMs was similar for patients in both arms of the trial with no statistically significant differences between treatment and placebo groups (EQ-5D, $p = 0.98$; EQ-5D VAS, $p = 0.88$; SF-36, $p = 0.94$, GQL-15, $p = 0.66$; GAL-9, $p = 0.87$). However, there were statistically significant differences between stable and progressing patients, as determined by visual fields, on glaucoma-specific PROMs (GQL-15, $p = 0.02$; GAL-9, $p = 0.02$) but not on general health PROMs (EQ-5D, $p = 0.62$; EQ-5D VAS, $p = 0.23$; SF-36,

p = 0.65). The findings suggest that PROMs, specifically those used in the UKGTS, may not be sensitive enough to detect clinical changes in glaucomatous disease. In addition, this study evidenced that the current instruments used to measure quality of life are unlikely to capture all consequences of glaucoma that are relevant to the patient. The results have implications for the design of future glaucoma clinical trials.

The work described in **Chapter 4** investigated the equivalence of measurement outcomes between patients attending a standard glaucoma care service, where patients see an ophthalmologist in a face-to-face setting, and a virtual glaucoma clinic. Average MD measurements for patients in the virtual clinic were compared against a 'big data' repository of patients attending a standard glaucoma care service, which was used to create expected limits. The total number of patients scoring outside the 90% expected limits was lower than what was allowed for, suggesting patients attending a virtual clinic have equivalent outcomes on the visual field test to patients in standard care. These results may help to lower the burden of hospital visits for patients with stable, early stage glaucoma.

In **Chapter 5**, experiences of only-eye surgery were investigated. In the study described in this chapter, qualitative interviews were carried out among both patients who have undergone surgical intervention on their only-eye, as well as surgeons performing these types of procedures. Interview transcripts were thematically analysed and generated a number of key themes relevant to only-eye surgery. For the surgeons, key themes included material risk, strategies for risk reduction, training, and the emotional impact of surgical complications. For the patients, themes related to the emotional impact of undergoing only-eye surgery, coping mechanisms, and how to improve care systems. This study was the first to assess experiences of only-eye surgery using a qualitative methodology and the results should inform future patient and professionals about the realities of these high-stakes surgeries.

6.2 Future work

The studies reported in this thesis go some way towards improving the understanding of the patient journey in glaucoma. Yet, these research outputs also raise a number of questions which have the potential to be addressed in future work. Specific ideas for future research relating to each individual chapter are discussed in the following section:

Chapter 2 demonstrated that the rate of decline in glaucoma patients' vision-related quality of life begins to slow after the MD in the better-eye is reduced to approximately -5dB. This slow decline remains apparent until better-eye MD is reduced to –dB or worse, whereby a rapid decline in vision-related quality of life occurs. However, we did not have data regarding the rate of visual field progression amongst the study participants, and this is likely to have an impact on vision-related quality of life. A future study whereby vision-related quality of life and better-eye MD are assessed longitudinally and evidence of a gradual then sudden decline are investigated would be an important addition to the literature. In addition, this analysis could be repeated using instruments other than the NEI VFQ-25, such as glaucoma-specific PROMs to look for evidence for decline in vision-related quality of life as glaucoma worsens.

Chapter 3 evidenced that group differences on PROM responses only emerge when comparing stable and progressing patients on instruments that are specific to glaucoma. Yet, PROM data were collected at only two time points, 24-months apart. Future research should be aimed at determining PROM sensitivity when measured at more frequent time points and over a longer duration. In addition, new methods of assessing patient-reported quality of life are being realised, such as the use of computer adaptive testing. Compared to traditional PROMs, computer adaptive testing requires fewer items to arrive at equally precise scores reducing test burden, and potentially enhancing validity and reliability. Currently, several item banks and computer adaptive tests for glaucoma are being constructed, but none are available for wide use (Khadka et al., 2015; Matsuura et al., 2017). Once available, replicating the study described in this chapter using computer adaptive testing will make for important future research.

Chapter 4 indicated that patients attending a virtual glaucoma clinic are likely to have similar measurement results on the visual field test as patients who are monitored in standard glaucoma clinics. Yet, the number of available measurements for the virtual

clinic patient cohort was quite small, where the average number of clinic appointments was three. At the time of conducting this study, the virtual glaucoma clinic was a relatively new addition at the hospital eye service where the data were collected. Future work should address questions regarding the equivalence of visual field outcomes over a longer duration of time. Furthermore, this study assessed only visual fields which is but one measurement of glaucoma status. Future work is needed to assess the equivalence between virtual and standard clinics on other measures of glaucoma disease.

Chapter 5 investigated the patient and surgeon experiences of only-eye surgery. This was an exploratory study with the aim to increase the understanding and improve the patient experience of only-eye surgery. Future work should aim to gain more perspectives from patients and surgeons about only-eye surgery, possibly through the use of questionnaire or survey methodologies. Furthermore, the research group involved with the study described in chapter 5 have planned a further study into the perspectives of high-stakes ocular surgery. For this study, a research proposal has been drafted (by LJ) relating to surgeon experiences of performing paediatric glaucoma surgery. The purpose and background of this proposed study are described in brief below.

Purpose and background of proposed investigation: Childhood glaucoma is a relatively uncommon, potentially blinding paediatric condition. The disease represents a significant public health concern due to the number of life-years potentially affected by the condition (Aponte et al., 2010). In the United Kingdom, the annual incidence of children being born with glaucoma is estimated to be approximately 1 in 18,500 births (Papadopoulos et al., 2007). Childhood glaucoma can have serious and significant implications on patients' development, education, and quality of life (DeCarlo et al., 2012).

The primary treatment for paediatric glaucoma is surgery (Taylor et al., 1999), and this is often performed during childhood years. The most commonly performed paediatric glaucoma surgery is goniotomy, whereby incisions are made in layers of the eye's tissue in an attempt to reduce intraocular pressure and slow the damage that is caused by glaucoma. The procedure requires careful surgical planning and patient positioning. The management of paediatric glaucoma can be challenging for the surgical care team. The success rate of surgery is variable, with success estimates ranging from 30-90%, depending on the age and ethnicity of the patient (Al-Hazmi et al., 2005; Chang et al.,

2017), and repeat procedures are often required. Complications are rare, but pose as a significant threat to the patients' remaining vision (Chang et al., 2017).

Figure 6.1: The authors named on this proposal are closely involved with promoting ophthalmic care and public health. The images shown on the right come from the educational project led by this research team entitled 'Prize your Eyes' whereby children were asked to reflect on the causes and impact of major eye disease.

Given the associated risks of surgery, coupled with the significant number of life-years at stake, a career as a paediatric glaucoma surgeon can be physically and psychologically demanding. Paediatric glaucoma surgeons will often have to shoulder the burden of negative surgical outcomes, as well as coping with reactions from family members, possible judgement from colleagues, and the possible threat of litigation or even disciplinary proceedings (Turner et al., 2016). It can be difficult to prepare ophthalmologists-in-training for the psychological sequelae of paediatric glaucoma surgery. Research indicates that self-reported intraoperative stress and anxiety is highest amongst surgeons when operating on complex or high-risk patients (Anton et al., 2015), and paediatric glaucoma surgery can often fit both these criteria. For that reason, we believe that research into how surgeons approach paediatric glaucoma surgery, such as the surgical logistics, and management of performance anxieties is warranted.

List of supporting publications

Peer-reviewed manuscripts

Jones L, Bryan S, Crabb DP. Gradually then suddenly? Decline in vision related quality of life as glaucoma worsens. *Journal of Ophthalmology*, 2017; Article ID 1621640.

Jones L, Bryan S, Miranda MA, Crabb DP, Kotecha A. Example of monitoring measurements in a virtual eye clinic using 'big data'. *British Journal of Ophthalmology*, 2018; 102: 911-5.

Jones L, Garway-Heath DF, Azuara-Blanco A, Crabb DP. Are patient self-reported outcome measures (PROMs) sensitive enough to be used as endpoints in clinical trials? Evidence from the United Kingdom Glaucoma Treatment Study. *Ophthalmology*, 2019; 125(5): 682-9.

Conference presentations

British Congress of Optometry and Vision Science (BCOVS) – Anglia Ruskin University 2018 - Cambridge, England – Oral presentation

Are patient-reported outcome measures sensitive enough to be used as endpoints in clinical trials – Evidence from the UK Glaucoma Treatment Study.

Lee Jones*, David Garway-Heath, Augusto Azuara-Blanco, David Crabb*

The Association of Research in Vision and Ophthalmology (ARVO) 2018 - Honolulu, HA - Poster presentation

High-stakes ocular surgery through the eyes of the surgeon: Experiences of operating on 'only-eye' patients.

Lee Jones*, Vinette Cross, Freda Sii, David Crabb, Peter Shah*

British Congress of Optometry and Vision Science (BCOVS) – University of Plymouth 2017 - Plymouth, England – Poster presentation

Example of monitoring measurements in a virtual eye clinic using 'big data'.

Lee Jones*, Susan Bryan, Marco Miranda, David Crabb, Aachal Kotecha*

United Kingdom and Eire Glaucoma Society (UKEGS) 2016 - Cheltenham, England – Oral presentation

Are patient-reported outcome measures sensitive enough to be used as endpoints in clinical trials – Evidence from the UK Glaucoma Treatment Study.

Lee Jones*, David Garway-Heath, Augusto Azuara-Blanco, David Crabb*

The Association of Research in Vision and Ophthalmology (ARVO) 2016 - Seattle WA 2016 - Oral presentation

Are patient-reported outcome measures sensitive enough to be used as endpoints in clinical trials – Evidence from the UK Glaucoma Treatment Study.

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Appendix 1 Indicative interview topic guide (Chapter 5)

Opening question:

For patients: I am interested to hear about your experience of having surgery on your (right/left) eye. Can you say a bit about how that came about?

For surgeons: I am interested to hear about your experiences of performing only-eye surgery. Can you say a bit about how these came about?

Examples of prompts that may be used as required:

Is there a time/moment/episode that stands out?

Can you reflect back on any high points/low points?

Is there anything in particular that changed how you saw things? Or how you acted?
Or felt?

Can you think of something that happened, which seemed trivial at the time, but which became more significant later?

Do you have a sense of any unfinished business about anything?

If you could go back in time to the beginning of this story and replay events, how might it be different?

Winding down:

Your story/ies have given me a fascinating insight into things. Do you think there is anything else I could have asked, or that you want to add?

If anything occurs to you afterwards, here is my email. I'd welcome further comments.

Appendix 2 Research Ethics Committee meeting attendance (attended by LJ), Research Ethics Committee, and Health Research Authority study approvals (Chapter 5)

NHS
Health Research Authority

London - Chelsea Research Ethics Committee
Research Ethics Committee (REC) Bristol Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Telephone: 020 7104 8052

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

19 October 2017

[redacted]
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Birmingham
B15 2TH

Dear [redacted]

Study title:	**Understanding the experience of only-eye surgery in glaucoma patients: a narrative inquiry**
REC reference:	**17/LO/1664**
Protocol number:	**RRK6025**
IRAS project ID:	**232559**

The Research Ethics Committee reviewed the above application at the meeting held on 09 October 2017.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact [redacted] outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

The Committee gave a favourable opinion of the application (with additional conditions)

1. Make the following changes to the Participant Information Sheet (PIS):
   a) Add a sentence to say the study is part of a PhD
   b) Change to a uniform font of a larger size
   c) Change the "why have I been chosen" section heading to "why have I been invited to take part in the study"
   d) Add a sentence to say that the audio recording would be destroyed after transcription
   e) IRAS A43 suggested that participants could be contacted "for additional information relating to the study at a later date" but there was no detail on how much later and for what type of information. The Committee requested that the term "additional information" was described in more detail along with making "at a later date" more explicit in the PIS.
2. Add a description of the dissemination event, as described to the Committee, to the protocol.
3. Add an additional, explicit statement clarifying the issues raised in point 1d to the Informed Consent Form.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Summary of discussion at the meeting

The Committee welcomed [redacted] to the meeting.

- **Social or scientific value; scientific design and conduct of the study**

The Committee queried how the study will ensure the samples are representative of the two populations - only-eye and clinicians.

[redacted] *confirmed that the only-eye population was small. He wanted to conduct intense interviews in small groups rather than have less time to interview larger groups of participants.* [redacted] *added that this was an initial study to establish scope and whether the approach was correct before a follow-up in which the key themes could be explored further.*

The Committee accepted the response.

The Committee stated that only-eye surgeries are usually performed as a last resort and by senior surgeons in many eye hospitals. The Committee asked who would be performing the surgeries considered in this study.

[redacted] *suggested that there would be a range at University Hospitals Birmingham NHS Foundation Trust. Some surgeons would have only done 1-2 operations whilst others would be very experienced and supervising other surgeons.*

The Committee accepted the response.

The Committee suggested that the study could consider matching the patient and surgeon and then they could see if their experiences matched.

[redacted] *indicated that the submitted study had two separate strands- one for patients (participants) and one for surgeons. He replied that the matched idea could be interesting but was not the study he wanted to undertake at this time.* [redacted] *added that the submitted study did not require the surgeon to be matched to the participant's surgery.*

The Committee accepted the response.

- **Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)**

The Committee queried the support that would be provided to participants who became distressed during the study.

[redacted] *indicated that the information was already in the PIS. He said the participant could contact the CI,* [redacted] *and there was also a contact independent of the study – PALS.* [redacted] *said that if a participant became distressed during the interview and wanted to stop, the participant could discuss the situation with him and, if appropriate, the removal of their data from the study.*

The Committee asked whether the support would include emotional support.

[redacted] *onfirmed it would.*

The Committee accepted this response.

- **Informed consent process and the adequacy and completeness of participant information**

The Committee were interested to know more about the planned dissemination event and asked the applicant to tell them more about the event.

[redacted] *replied that the event would be held after completion of all the interviews and the analyses. He would invite all the participants back for the dissemination event in which they would come together, could interact and discuss their experiences of being part of the research.*

The Committee suggested details of the dissemination event should also be added to the protocol.

The Committee asked whether the interviews would be conducted at the hospital.

[redacted] *confirmed they would be in the hospital.*

The Committee accepted the response.

- **Other general comments**

The Committee noted that IRAS A43 suggested that participants could be contacted "for additional information relating to the study at a later date" but there was no further detail on how much later and for what type of information. The Committee requested that the term "additional information" was described in more detail in the PIS along with making "at a later date" more explicit. The Committee requested that an additional, explicit statement clarifying these issues was added to the Informed Consent Form.

The Committee noted that the Participant Information Sheet (PIS) did not include a sentence to say the study was part of a PhD.

The Committee noted that the PIS did not include a sentence to say that the audio recording would be destroyed after transcription.

The Committee noted the mixture of fonts in the PIS and requested they were made uniform and a larger font was used for this study population.

The Committee requested that the "why have I been chosen" section heading was changed to "why have I been invited to take part in the study".

The applicant left the meeting.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]	1.0	23 August 2017
Interview schedules or topic guides for participants [Interview guide]	1.0	25 August 2017
IRAS Application Form [IRAS_Form_15092017]		15 September 2017
IRAS Application Form XML file [IRAS_Form_15092017]		15 September 2017
IRAS Checklist XML [Checklist_15092017]		15 September 2017
Letters of invitation to participant [Invitation letter]	1.0	31 July 2017
Participant consent form [Consent form]	1.0	31 July 2017
Participant information sheet (PIS) [Participant information sheet]	1.0	31 July 2017
Research protocol or project proposal [Research protocol]	4.0	07 September 2017
Summary CV for Chief Investigator (CI) [CI Summary CV]	1.0	23 August 2017
Summary CV for student [Student CV]	1.0	08 March 2017
Summary CV for supervisor (student research) [Supervisor CV]	1.0	09 September 2017
Validated questionnaire [Questionnaire]	1.0	31 July 2017

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

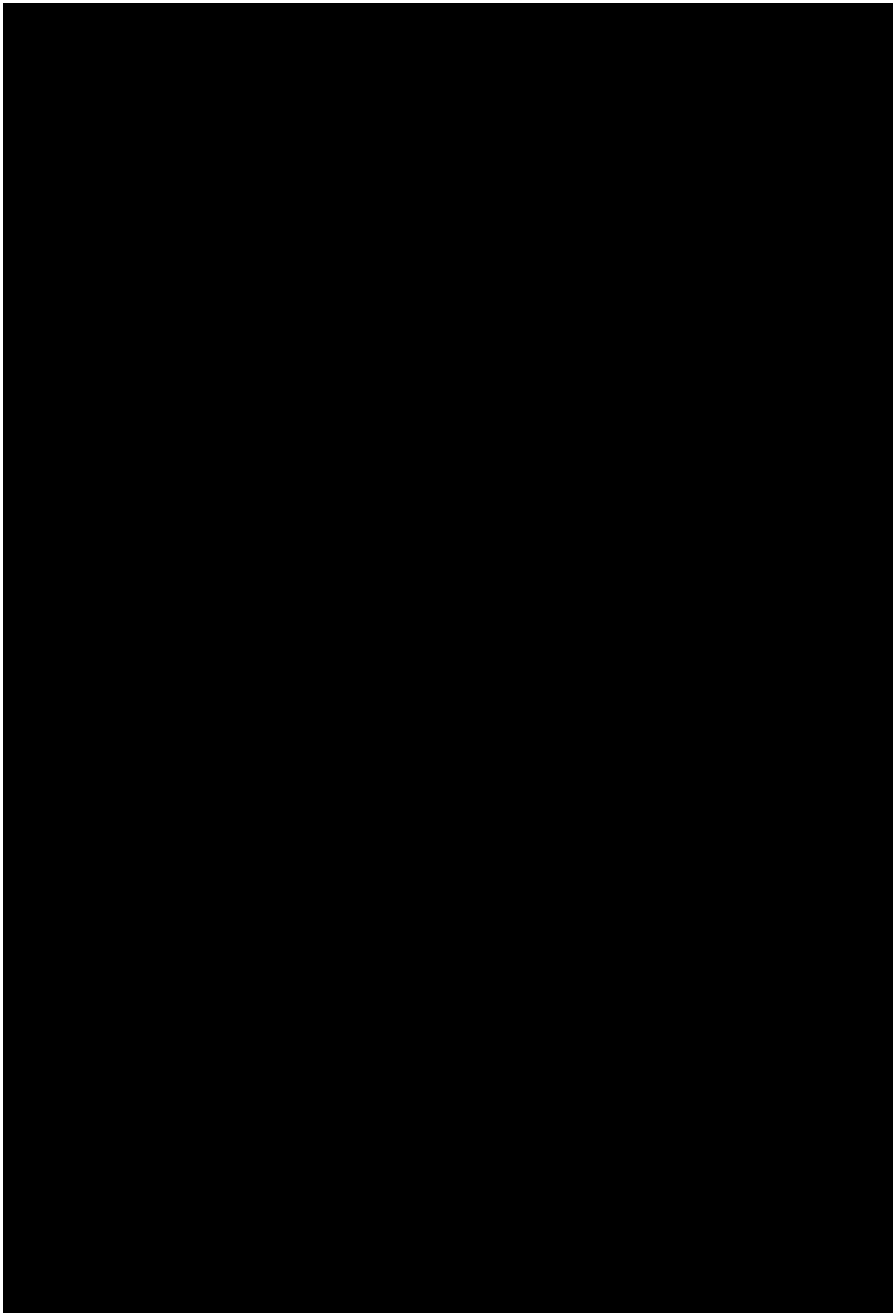
17/LO/1664	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely
PP

London - Chelsea Research Ethics Committee

Attendance at Committee meeting on 09 October 2017



Health Research Authority

London - Chelsea Research Ethics Committee
Research Ethics Committee (REC) Bristol Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Telephone: 020 7104 8052

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

30 October 2017

[redacted]
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Birmingham
B15 2TH

[redacted]

Study title:	**Understanding the experience of only-eye surgery in glaucoma patients: a narrative inquiry**
REC reference:	**17/LO/1664**
Protocol number:	**RRK6025**
IRAS project ID:	**232559**

Thank you for your letter of 26th October 2017. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 19 October 2017

Documents received

The documents received were as follows:

Document	*Version*	*Date*
IRAS Checklist XML [Checklist_26102017]		26 October 2017
Participant consent form [Consent form]	2.0	19 October 2017

Participant information sheet (PIS) [Participant information sheet]	2.0	19 October 2017
Research protocol or project proposal [Research protocol]	5.0	19 October 2017

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]	1.0	23 August 2017
Interview schedules or topic guides for participants [Interview guide]	1.0	25 August 2017
IRAS Application Form [IRAS_Form_15092017]		15 September 2017
IRAS Application Form XML file [IRAS_Form_15092017]		15 September 2017
IRAS Checklist XML [Checklist_26102017]		26 October 2017
Letters of invitation to participant [Invitation letter]	1.0	31 July 2017
Participant consent form [Consent form]	2.0	19 October 2017
Participant information sheet (PIS) [Participant information sheet]	2.0	19 October 2017
Research protocol or project proposal [Research protocol]	5.0	19 October 2017
Summary CV for Chief Investigator (CI) [CI Summary CV]	1.0	23 August 2017
Summary CV for student [Student CV]	1.0	08 March 2017
Summary CV for supervisor (student research) [Supervisor CV]	1.0	09 September 2017
Validated questionnaire [Questionnaire]	1.0	31 July 2017

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

17/LO/1664 **Please quote this number on all correspondence**

Yours sincerely

[redacted]

[redacted]

Copy to:

[redacted] *University Hospital Birmingham NHS Foundation Trust*

NHS
Health Research Authority

[redacted]
Consultant ophthalmic surgeon
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way, Birmingham
B15 2TH

Email: hra.approval@nhs.net

30 October 2017

[redacted]

Letter of HRA Approval

Study title:	**Understanding the experience of only-eye surgery in glaucoma patients: a narrative inquiry**
IRAS project ID:	**232559**
Protocol number:	**RRK6025**
REC reference:	**17/LO/1664**
Sponsor	**City, University of London**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.