TRENDS AND HEALTH ECONOMIC ASPECTS OF SERVICE DELIVERY OF GLAUCOMA

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Abbreviations

AAG	Acute Angle Closure Glaucoma
ALT	Argon Laser Trabeculoplasty
AMD	Age Related Macular Degeneration
ARVO	Association for Research in Vision and Ophthalmology
BCOVS	British Congress of Optometry and Visual Science
BIPQ	Brief Illness Perception Questionnaire
CAI	Carbonic Anhydrase Inhibitors
CBA	Cost Benefit Analysis
CCT	Central Corneal Thickness
CDR	Cup Disc Ratios
CEA	Cost-Effectiveness analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEP	Cost Effectiveness Plane
CER	Cost Effectiveness Ratio
COAG	Chronic Open Angle Glaucoma
CUA	Cost-Utility Analysis
dB	Decibel
DES	Discrete Event Simulation
DS-14	Type D Personality Scale
DSA	Deterministic Sensitivity Analysis
DVLA	Driver and Vehicle Licensing Agency

EGS	European Glaucoma Society
EQ-5D	EuroQol 5 Dimension
GAT	Goldman Applanation Tonometry
GDP	Gross Domestic Product
GHT	Glaucoma Hemifield Test
HFA	Humphrey Field Analyzer
ICER	Incremental Cost Effectiveness Ratio
IOP	Intraocular Pressure
IPIG	Illness Perception in Glaucoma
IPQ	Illness Perception Questionnaire
IPS	International Perimetry Society
IVF	Integrated Visual Field
MD	Mean Deviation
NBA	Net Benefit Approach
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSC	National Screening Committee
NTG	Normal Tension Glaucoma
OECD	Organisation for Economic Co-operation and Development
OHT	Ocular Hypertension
PGA	Prostaglandin Analogue
POAG	Primary Open Angle Glaucoma

PROMS	Patient Reported Outcome Measures
PSA	Probabilistic Sensitivity Analysis
PSD	Pattern Standard Deviation
QALY	Quality Adjusted Life Year
QIPP	Quality, Innovation, Productivity and Prevention challenge
RCT	Randomised Controlled Trial
RGC	Retinal Ganglion Cells
SAP	Standard Automated Perimetry
SF-6D	Short Form 6 Dimensions
SG	Standard Gamble
SLT	Selective Laser Trabeculoplasty
TTO	Time Trade Off
UKEGS	UK and Eire Glaucoma Society
VAS	Visual Analogue Scales
VF	Visual Field
WTP	Willingness to Pay

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Declaration

The work contained in this thesis was completed by the candidate, Trishal Boodhna. It has not been submitted for any other degrees, either now or in the past. Where work within this thesis has been previously published, statements regarding this has been made within the text. All sources of information used within this thesis have been suitably acknowledged with references being given.

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List of Supporting Publications

The work reported in Chapter 2 was published as a Chapter within an NIHR report titled "*Frequency of visual field testing when monitoring patients newly diagnosed with glaucoma: mixed methods and modelling*", (Crabb et al., 2014) for which Trishal Boodhna was the main analyst and author under the supervision of Professor David Crabb and in collaboration with Richard R. Russell(1).

The work published in Chapter 3 was reported in *Ophthalmic and Physiological Optics* (Boodhna et al., 2014) for which Trishal Boodhna was the main analyst and author under the supervision of Professor David Crabb(2).

The work published in Chapter 4 was reported in *Eye* (Boodhna et al., 2015) respectively under the supervision of Professor David Crabb with collaboration from Luke J. Saunders(3).

The results of Chapters 3 and 4 have been presented in part at the following conferences:

- Association for Research in Vision and Ophthalmology (ARVO) Meeting, Fort Lauderdale in May, 2014 (oral presentation)
- British Congress of Optometry and Visual Science (BCOVS), London in September, 2015 (oral presentation)
- UK and Eire Glaucoma Society (UKEGS) Meeting, Edinburgh in December, 2012 (poster presentation)
- UK and Eire Glaucoma Society (UKEGS) Meeting, Bristol in November, 2014 (oral presentation)
- International Perimetry Society (IPS) Meeting, New York in September, 2014 (oral presentation)

The work described in Chapter 5 has published in *BioMed Central: Health Service Delivery* (Boodhna et al., 2016) for which Trishal Boodhna was the main author under the supervision of Professor David Crabb(4).

Abstract

Glaucoma describes a group of optic neuropathies characterised by progressive irreversible loss of visual function. Within this thesis, a health economic model was constructed to map service provision from diagnosis considering two competing strategies: the current practice of annual visual field (VF) monitoring against the proposed guidelines of performing 6 VFs in the first two years. The constructed model found the proposed practice to be cost effective at a willingness to pay ceiling ratio of £30,000 per quality adjusted life year (QALY), identifying an incremental cost effectiveness ratio (ICER) of £21,679. The findings of the model however were potentially sensitive to the modelled infrastructure improvement costs required to undertake the proposed guidelines and a costing study to more accurately ascertain these costs was recommended.

Following this study, statistical analysis of 473,252 VFs was undertaken to investigate trends in initial identification and progression rates whilst also narrowing their parameters within the health economic model. Consequently, the average level of glaucomatous vision loss at diagnosis was found to be improving by 0.11 dB per year on average whilst proportions of patients with 'advanced' loss at diagnosis fell significantly from 30% to 21%. Average progression rates were found to have fallen from -0.11 dB per year to -0.06 dB per year whilst average rates of loss in older eyes (>70 years) were found to progress faster than in younger eyes (<60 years). Furthermore, testing frequency was found not to vary by visual impairment risk factors. The constructed health economic model was subsequently updated to incorporate the more narrowly defined parameter distributions whilst also being re-specified to incorporate societal costs of visual impairment to count the true costs of the disease. This resulted in an improved ICER of £11,382.

In conclusion, it is likely that implementing the proposed guidelines of 6 VFs in the first two years is more cost-effective than annual monitoring. This argument is further reinforced once societal costs are accounted for however a scoping study to examine the required costs of improving the glaucoma monitoring infrastructure is required.

Chapter 1: Introduction

1.1 Healthcare Provision in the UK

1.1.1 The NHS

Healthcare in the UK is delivered by the National Health Service (NHS), a service established in 1948 in order to bring hospitals, doctors, nurses, pharmacists, opticians and dentists under one organisation(5). Prior to its creation, patients were required to pay for their healthcare or to rely on voluntary hospitals to provide them with free healthcare. Now, healthcare provision is funded by taxation with richer members of society effectively subsidising the access of poorer people to healthcare. Alternative sources of funding for the NHS also exist with the most notable being charges to patients for prescriptions and dental work(6). Private healthcare is also available to those who wish to bypass NHS waiting lists and instead seek potentially more personalised care. Specific treatments such as certain cosmetic surgeries are not available on the NHS and are therefore only available through private providers. There can potentially be long waiting lists to access NHS resources although patients wishing to access immediate care can do so by visiting a private healthcare provider. The constitution of the NHS formalises the rights of the patients and staff in addition to the public as a whole and establishes the principles that underpin the foundations of the NHS, allowing it to operate effectively and in equity. All bodies working under the NHS umbrella, whether public or private, have to abide by these principles by law and consider the constitution in all decisions and actions(7).

1.1.2 National Institute for Health and Care Excellence

One of the key principles within the constitution of the NHS legislates for the cost effective service provision of healthcare in the UK(7). The service should therefore seek to achieve the best value for money possible for UK taxpayers. A body within the Department for Health was therefore required to ensure that the pathways of treatment undertaken by patients represented the most efficient interventions available, resulting in the establishment of the National Institute for Health and Care Excellence (NICE) in

England and Wales. NICE was set up in its earliest form in 1999 and has grown in size and scope from simple health outcome measurement to undertaking health technology appraisals that legally oblige the NHS to provide interventions that have been validated by NICEs technology appraisal board(8).

There have been considerable benefits associated with introduction of NICE within the NHS organisational structure. Greater transparency is associated with NICE as it is fully independent of governmental oversight in addition to the lobbying power of both the pharmaceutical industry and special interest groups. NICE base their appraisals solely on the clinical and cost effectiveness of the intervention although exceptions can be made where the intervention provides supply to previously unmet demand(8). NICE also seeks to ensure a minimum standard of care is provided within the NHS by establishing clinical guidelines representing the most appropriate treatment strategies for differing conditions. The Guideline Development Group within NICEs structure, consisting of clinicians and patient representatives, considers both the medical interests of the patient and the economic arguments with relevant stakeholders(9). The guidelines provide information to both the clinician and the patient as to how their care pathway may be traversed, therefore increasing transparency in service provision. Transparency has been of increasing importance in recent years given, for example, the growing concern surrounding so called “postcode lotteries” in the UK. These arise where interventions are provided by certain regional health authorities but not by others due to local budgetary concerns, resulting in a disparity in service provision by differing regional health services(10). By introducing clinical care guidelines however, patients are not solely dependent on the clinician who may be influenced by the regional health authority to reduce access to care due to their financial state.

There is a growing argument however that the NICE guidelines have created some unintended inefficiencies in service delivery. By creating these clinical guidelines, there is potential for over referral as clinicians are less willing to use their intuition and personal judgements, contributing to a growing burden on resource consumption within the NHS. For example, in health service delivery for the eye disease glaucoma, the subject of this thesis, studies have found falling positive predictive values for glaucoma or glaucoma suspects following the introduction of the NICE guidelines(11-13). This has consequently resulted in growing calls to further refine existing NICE guidelines on glaucoma detection

and management in order to ensure those consuming finite NHS resources are those most likely to progress to a state of visual impairment within their lifetime(14, 15) .

1.1.3 The Current Financial Status of the NHS

The NHS has been under growing economic scrutiny in recent years given the financial status of the UK economy in general. At the time of writing, the UK economy is currently running an annual budget deficit, implying that it is spending more than it accrues in revenues, amounting to around £90bn (4.9% of GDP), one of the highest within the OECD(16). To rectify this, the current UK government is seeking to run budget surpluses and to use these to pay off a proportion of its national debt. In order to run at a budget surplus, certain non-protected governmental departments such as defence, local government and work and pensions departments have faced spending cuts. The NHS however is a protected department and while the public health budget is being cut, the NHS budget itself will not be negatively impacted. NHS funding in fact is predicted to expand by £8bn in real terms by 2020-21(16), a necessary expansion in expenditure given a projected increase in demand for services due, in part, to population growth and growing proportions of elderly members of society who tend to consume more healthcare(17, 18). Furthermore, this growth in funding comes with the caveat of a demand for the delivery of an effective "7 day service" to be provided by both NHS trusts and GPs(16). As such, a growing squeeze on NHS finances is being observed with demands for maximal efficiency gains being made in order to ensure the expansion in provision can occur without a reduction in the existing quality of care.

Monitor, an executive non-departmental public body of the Department of Health which regulates health services in the UK, has stated that due to growing demand for healthcare in the UK, the NHS faces a £30bn shortfall in funding by 2020/21(19). Year on year, the *Office for Budget Responsibility* have estimated efficiency gains within the NHS at 0.8% annually. Yet this rate of gain will not be sufficient to fulfil the current goals of expanded service provision given current spending constraints(20). As such, Monitor stated an ambition for a 2-3% annual net efficiency gain over the next 10 years. In order to achieve this, Monitor indicated that it requires investment in new care models in addition to poorer performing providers partnering with more efficient providers in order to help implement more effective and efficient care provision(19). The Kings Fund

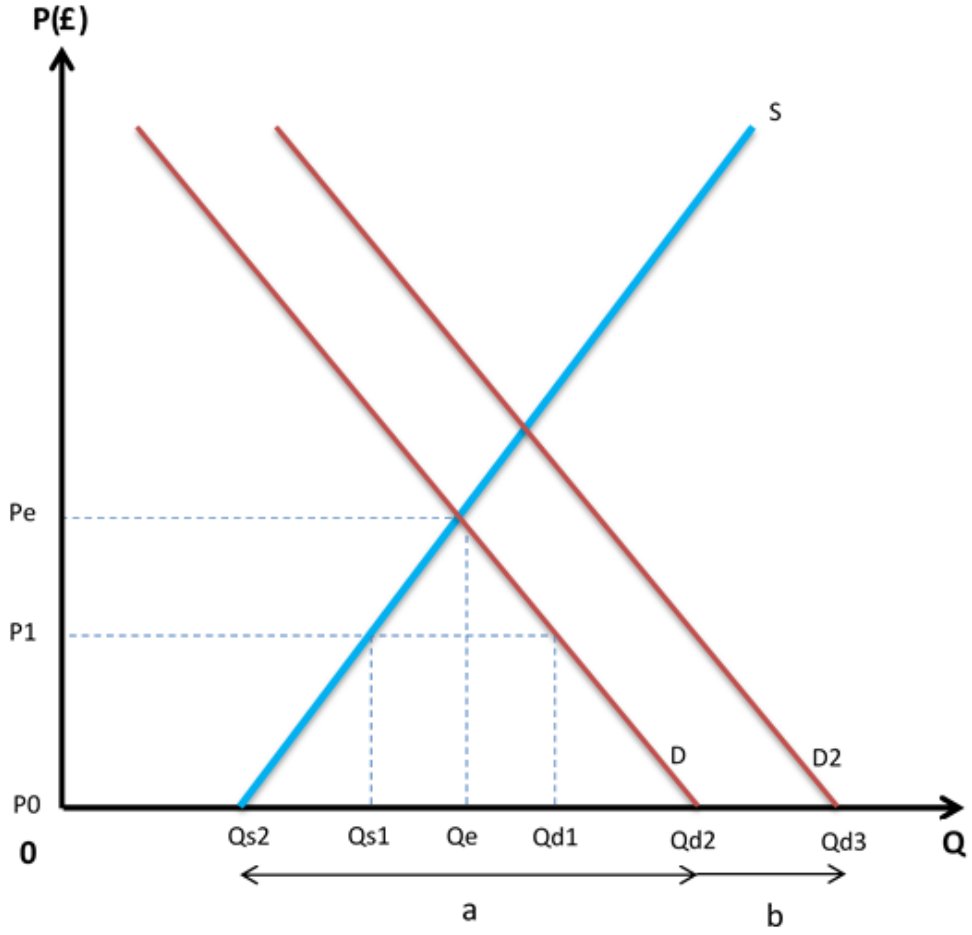
Quarterly Monitoring report on the financial performance of NHS foundation trusts in 2014/15 painted a bleaker picture of finances within individual NHS organisations also finding financial performance to be declining with an overall net deficit of £349m identified(21). As such, the Kings Fund projected a deepening crisis on the horizon for the NHS if a significant growth in funding was not to occur or if increasing efficiency gains were not achieved beyond those of the quality, innovation, productivity and prevention challenge (QIPP)(22). This has led the King's Fund amongst others to argue in favour of increasing the momentum of movement to incorporate aspects of health economics within healthcare provision in the UK(23-25).

1.2 Health Economics

1.2.1 Health Economic Theory

Given the finite nature of resources and the continuously expanding demands being placed on healthcare systems, it is unsurprising that concepts within the field of economics have been increasingly fused with the concepts of welfare provision. This has resulted in the development of the field of health economics: a framework that seeks to examine healthcare as if it was any other producible commodity. Decisions are required to be made about where resources should be used in order to efficiently produce this commodity as considerable opportunity costs exist. These opportunity costs are defined as the foregone opportunities that exist due to the selection of an alternative(26). For example, using NHS funding to invest in a nationwide screening program for prostate cancer in the UK may yield increased life expectancies of males over 50 years of age. This however means that resources may not be available for other cancer screening programs due to the finite nature of resources within the NHS. This zero-sum game represents the opportunity cost of undertaking the screening program for prostate cancer, the opportunity that has been foregone as a result of decision making. Given the considerable implications on the public of these choices, it is vital that a validated framework is utilised to inform appraisals of the cost-effectiveness associated with them.

Figure 1-1: Supply and Demand diagram for the 'market' for healthcare in the UK



Given the NHS provides healthcare free at the point of delivery, there is unconstrained demand for its services. Priority in service provision therefore has to be established in order to ensure those in the most need are provided with health care interventions in the most expedient fashion. Figure 1-1 represents the market for healthcare in the UK and the derivation of waiting lists graphically illustrated within a supply and demand diagram. Here, the Y-axis represents the price for healthcare and the X-axis represents the quantity of healthcare supplied. As the price of healthcare falls, the resultant quantity of healthcare that consumers demand would increase, therefore the demand curve is downward sloping (D). Conversely, as the price of healthcare increases, producers are more willing to supply healthcare to the market, therefore the supply curve is upward sloping (S). An equilibrium price in a normal, competitive market is found where the two curves intersect, where demand equals supply. This represents a hypothetical point of agreement between consumers and producers with a price that consumers are happy to pay (Pe) and a quantity that producers are happy to supply (Qe). This competitive market

equilibrium is achieved through market clearing, otherwise known as Adam Smith's "invisible hand"(27). For example, if the price for the commodity is below the market equilibrium (P1), suppliers would be less willing to make the commodity available for purchase (Qs1) whilst more consumers would demand the commodity (Qd1). The resultant scarcity in the market (demand > supply) would therefore drive prices upwards and suppliers will be increasingly willing to produce the commodity. This increase in supply will continue until the point is reached where producers and consumers agree on an equilibrium price (Pe) and therefore an equilibrium quantity supplied (Qe) and the scarcity is cleared (demand = supply). The healthcare market in the UK however is different to that of a normal commodity due to the presence of the NHS. The market price for healthcare in the UK at the point of delivery is free (P0), and we therefore have scarcity in the market as demand exceeds supply (Qd2 > Qs2). Consequently, rationing occurs in order to ensure supply is provided to those in most desperate need, resulting in waiting lists (a). As populations age and expand however, demand for services expand (D>D2), scarcity increases and so does rationing and waiting lists (a+b). Therefore, in order to maintain the level of service year on year, supply needs to expand at the same proportion that demand expands and this can be achieved by increasing the amount of healthcare infrastructure and NHS staff that provide care or by increasing efficiency in service provision.

Given trends in population growth, it should be unsurprising that efficiency is a key health economic concept. The allocation of resources towards the most effective production processes results in allocative efficiency, otherwise known as Pareto efficiency. This form of efficiency stems from the comparison of competing treatments or strategies in order to ascertain which would represent the best return given resources employed. In terms of economic efficiency, health economics attempts to examine the costs associated with resource use in the production of healthcare and seeks to incorporate these factors into the decision making process. The interested reader can find out more about the general principles of Health Economic theory elsewhere(28).

1.2.2 Measurement of Quality of Life

Since cost-effectiveness evaluation measures the benefits of interventions relative to their costs, the accurate quantification of the improvements in quality of life associated

with them are vitally important. Inexact measurement would lead to poor estimation of associated quality of life impacts leading to erroneous conclusions being drawn. Accurate quantification of quality of life however is difficult to achieve due to the varying nature of patient perception of wellbeing. For example, the same degree of pain may be quantified differently by two different people suffering from the same condition due to differing pain thresholds between them. Alternatively, people may differ in their general perception of quality of life due to their personality traits. Certain individuals may be classified as Type-D (distressed), consequently resulting in a gloomier perception of their quality of life(29), therefore potentially reporting lower quality of life.

The development of the quality adjusted life year (QALY) in recent years has aided the process of economic evaluation in glaucoma. The QALY seeks to provide a numerical and comparable interpretation of the quality and quantity of life lived. Comparison of QALYs quantifies effectiveness of treatments in units of utility representing wellbeing whilst also taking into account adverse side effects. It is possible to establish the cost per QALY derived for a treatment by analysing the resources the treatment requires. This in turn allows cost-effectiveness of a treatment relative to its alternatives to be established. Simply put, the cost per QALY is calculated by dividing treatment costs associated with the intervention by the quantity of QALYs gained by it.

There are certain requirements that need to be fulfilled by questionnaire respondents before utility calculation can be accurately ascertained. They are required to be utility independent and risk neutral as violations may lead to response bias. Respondents are also required to be consistent and to display rational trade-off behaviour. Violations of these requirements can lead to issues with QALY quantifications and these are potentially exacerbated by underlying flaws that can exist in the use of QALYs in relation to certain types of conditions. For example, a QALY gained by providing an intervention for erectile dysfunction is not equivalent to a QALY gained through dialysis to avoid renal failure as one improves quality of life whilst the other prolongs it. Cost-effectiveness analysis equates them on a unitary basis however, therefore the lack of attribution of societal value of the QALY could lead to misleading health policy decisions(30). Issues arise however when the population used to quantify QALYs associated with a condition suffer from it themselves. Volk and colleagues questioned 10 otherwise healthy male participants aged 56 years on average about how erectile dysfunction may impact their quality of life. A reduction of utility of 0.26 was identified however when their wives were

questioned their responses were different with a value of 0.02 identified despite the fact that they could equally be impacted by the erectile dysfunction(31). As such, it is important to understand the psychosocial interaction within QALY calculation as values may be over stated as a consequence. It has therefore been argued that those with the condition are best placed to comprehend the impact of the condition and, as such, people without experience of the condition should not be used to quantify QALYs. Issues arise out of this however as those with the condition may be bias towards exaggeration of quality of life impacts if they are aware that their feedback may have consequence upon their access to treatment. Furthermore, it could also be argued, given that society funds the NHS in the UK via taxation, societal value for the impact of the condition should be accounted for, thus arguing in favour of QALY estimation based on healthy non-patients.

There are alternatives available to quantify quality of life beyond the QALYs and one such method is the quantification of disability-adjusted life years (DALYs), frequently used by the World Bank and the World Health Organisation(32). They are similar to QALYs in that they are both measures of health adjusted life years however, whilst QALYs measure health gains associated with interventions, DALYs measure the burden of disease. DALYs incorporate age-weighting and discounting of future values within their calculations and rather than applying measures of quality of life to different health states they apply these measures to discrete states of wellbeing(33). Age weighting has been argued to be controversial however as it argues that a young adults life is more valuable than an older adult or a child's life whilst the use of instrumental value has been found to weight in favour of higher wage earners(34). There consequently remains debate over which quantification method is preferable, with understanding of the systematic differences between the two methods required when deciding which approach to choose(32, 35, 36).

1.2.3 Tools for the Measurement of Quality of Life

There are different methods available to the analyst seeking to quantify the amount of QALYs associated with different states of wellbeing. One such method is the 5 dimension EuroQol questionnaire (EQ-5D)(37). The intention of the questionnaire is for respondents to self-report their quality of life; it can be used in surveys and interviews alike and is easily implemented given its relatively short and simple nature. The EQ-5D has been chosen as the preferred method of QALY estimation in adult populations by the NICE

Methods Guidance on Methods in Technology Assessment(38). The key reasoning behind this is the generalisability of the instrument, the outcomes associated with them can be cross-compared irrespective of potential differences in medical arena. It has been noted however that the EQ-5D is not intended to measure all aspects of health related quality of life in complete detail and that disease specific instruments should be utilised in combination with the EQ-5D for truly representative QALYs(39). The EQ-5D however has been criticized for having low sensitivity to improvements related to conditions with low morbidity whilst also not being responsive enough to identify small changes in health(40-42). An alternative to the EQ-5D is the SF-6D, an instrument derived from the SF-36 but with added ability to incorporate preferences into its scoring. This tool describes 1,800 health states in total and does so by conversion of SF-36 measurements using preference weights identified from the UK general population. The SF-6D is not without its limitations too however as it has been found to overestimate the value of the worst health states in addition to not being responsive to changes in those conditions that experience high morbidity(40).

Beyond questionnaires, health and behavioural economists have identified alternative methods of preference elicitation. The Standard gamble (SG) method, first presented by von Neumann and Morgenstern(43), measures preferences within the presence of uncertainties. With this method, participants are presented with two choices with the first being a certain state of health (for example frequent bouts of angina) and the second being a gamble between a better state of health (for example no angina) or worse (for example death). The participants are then requested to state the required probability of the improved outcome for them to be indifferent of the first or the second choice. Therefore, if a probability of 75% was stated as making them indifferent between the two, 0.75 would represent the utility. Given the way SGs are formulated they therefore are potentially impacted by the risk seeking nature of the respondent and therefore need to be undertaken by risk neutral individuals. The time trade off (TTO) method asks participants to consider the amount of time they would be willing to sacrifice in order to avoid a certain worse health state(44). If the respondent is provided with a 10-year time scale and they indicate that they would be willing to sacrifice 3 years that would leave them with 7 years remaining. As 70% of the original time scale, their utility score for the condition would be 0.7. TTO incorporates a certain outcome compared to the gamble associated with SGs, making the SG method likely to overestimate utility when risk averse respondents are utilised. A further preference elicitation method available is the use of

visual analogue scales (VAS). These are based on psychometric theory and consist of a single line incorporating anchors indicating the best and worst possible health. Participants are then required to place the different health states on this interval scale indicating perceived differences. These scales are often used to complement the SG and TTO methodologies although it has been argued that VASs have significant benefits over them(45).

1.2.4 Economic Evaluation

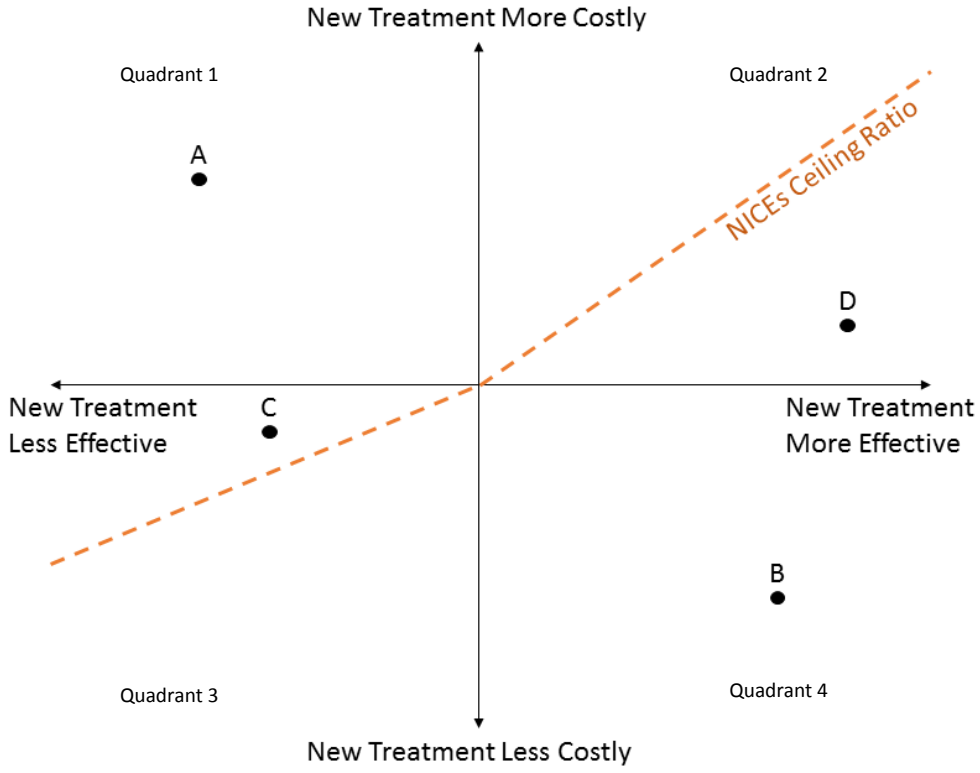
Economic evaluation creates a systematic framework for the comparison of quality of life measurements relative to the costs associated with implementing the associated interventions. Economic evaluations take a generally similar structure and require the measurement of costs and benefits associated with competing treatments or clinical strategies. They can be undertaken in conjunction with clinical trials but can also be implemented through existing medical literature. Clinical trial lengths are often prohibitive and costly(26) and are factors which have given rise to cost-effectiveness evaluation and modelling. There are four main types of economic evaluation, varying either in terms of how costs are quantified, how benefits are quantified and the assumptions that underpin their calculation:

1. Cost-Effectiveness Analysis

Cost-Effectiveness analysis (CEA) examines the outcomes associated with two different treatments relative of the costs derived to gain them. Costs are established in monetary terms with benefits measured in an alternative unit. An Incremental Cost Effectiveness Ratio (ICER) is then established to represent the cost of gaining an increased unit of benefit and is calculated by dividing the differences in costs between the interventions by the difference in effectiveness(26). For example, treatment A may cost an extra £100k compared to treatment B. If the outcome associated with treatment A yields an increased benefit of 5 QALYS over B, an incremental cost effectiveness ratio (ICER) of £20,000/unit is derived. If this ICER is below the willingness to pay threshold of the payer, then treatment A will be preferred to B and vice versa if the ICER is above the threshold. There

are various decision rules that exist within cost-effective analyses which can be illustrated using a cost effectiveness plane (CEP).

Figure 1-2: The Cost-Effectiveness Plane



The CEP (see Figure 1-2) is a plane split into four quadrants and plots the ICER according to whether the alternative is costlier and/or more effective than the current intervention. When the alternative is dominated due to being costlier and less effective (quadrant 1) it is represented by point such as A, with the alternative therefore being rejected. The alternative can dominate over the original treatment and therefore be preferred in the instance that the roles are reversed with costs being lower and effects being higher with the alternative (quadrant 4) such as point B. Quadrant 2 and 3 illustrate more complicated outcomes than 1 and 4 however. These represent areas of the plane where the alternative is either less costly and less effective (quadrant 3) or costlier and more effective (quadrant 2), therefore a further decision rule must be employed. A willingness to pay decision rule is required as to what ratio of costs to increased benefit is acceptable with a willingness to accept ratio is also required to identify the acceptable ratio of

reduced benefit to reduced costs. An ICER represented by point C for example is likely to result in a rejection of the alternative despite the lower costs associated with it as it represents significantly lower effects for the patient. An ICER represented by point D however is likely to result in an acceptance of the alternative as the costs are only marginally higher and the effects are significantly larger than the comparator. Therefore, the ratio of costs to benefits is within the scope of the payer's willingness to pay. The identified ratio can be indicated by a straight line running from the origin of the plot. Points above this line are likely to get rejected as they represent an area above the willingness to pay or accept ratio. Conversely, ICERs below this line will be accepted for being below this ratio. The line is observed to kink when traversing over the origin as payers are less willing to pay for a reduction in effects and costs than they are willing to pay for an increase in effects and an increase in costs, consequently requiring a higher cost benefit ratio(46). As such, a lower CER ceiling ratio exists in quadrant 2 compared to quadrant 3, indicted by the lower slope. Study of NICEs past decision making have found that this ceiling ratio is quantified at £20,000 to £30,000 for every extra QALY derived(47), indicated by the kinked ratio line in Figure 1-2.

2. Cost-Utility Analysis

Cost-Utility analysis (CUA) is similar to CEA analysis but instead examines the outcomes of interventions relative to a measurement of utility. This unit of measurement refers to the subjective level of wellbeing that people experience relative to differing levels of health states and is usually based upon the QALY(48). Costs are established in monetary units whilst benefits are expressed using the QALY. QALYs are argued to be a better indicator of improved outcomes compared to the units of measurement usually used in CEA as they relate directly to the wellbeing of the individual. Furthermore, the use of the QALY allows for the cross comparison of differing conditions with different improvements in patient outcomes given their analysis of uniform units(26). A drawback of this methodology however is that societal costs are often not taken into account when this method of evaluation is employed. For example, whilst the cost of visual impairment to the individual may be accounted for in a CUA, the costs to society of rehabilitation, environment adaptation and disability payments may not be accounted for. Consequently, benefits beyond the patient such as benefits to the patient's family or to the productivity of society are not accounted for in CUAs. It is also argued that QALYs are

significantly more difficult to estimate than the monetary gains associated with treatment, with the resulting uncertainty clouding the findings of these studies.

3. Cost-Benefit Analysis

The cost benefit analysis (CBA) approach measures costs and benefits in monetary terms with both costs and benefits measured in the same units in order to be accurately assessed against one another(26). The measurement of benefit within a similar to framework to that of costs represents a significant issue however is it requires translating patient derived utility into monetary units. One measurement of treatment outcomes can be undertaken using either the human capital methodology or contingent valuation methodology. The human capital method relies on the individual being seen as a productive form of capital and as such is measured in terms of productivity, usually represented by their salary. Consequently, the benefits of treatment can be measured as being related to the discounted future income that would potentially have been foregone as a result of non-treatment. Contingent valuation seeks to establish monetary value related to the benefits associated with the consumption of a commodity that is not currently available in the market. In order to do so, this form of valuation requires the construction of a hypothetical situations and questions in the form of questionnaires which allow respondents to convey preferences and their willingness to pay (WTP). There are various different methods within which these situations can constructed with simple open-ended questions generally avoided due to the subjective nature and reduced accuracy of response analysis. The take it or leave it (TIOLI) method utilises the presentation of an option paying a certain amount for a commodity, therefore giving the respondent a concrete decision making criteria that they can take or leave and is an efficient method but requires large sample sizes to achieve significance. Alternatively, bidding games can be utilised to extract valuation by using the TIOLI structure but going further by raising or lowering the TIOLI amount to establish a threshold value. Finally, the check box method offers the respondent a series of values which require them to check a box which represents their valuation although this method is subject to range bias where respondents tend towards middle values in the options provided(49).

CBA and the decision rules that they generate are focused are ultimately focussed upon which intervention has the higher net benefit; the analyst then has the advantage of

being able to identify which treatments and strategies result in an aggregate gain to society, something that is not possible with the CEAs and CUAs. The CBA approach therefore allows the analyst to measure outcomes in terms of absolute costs rather than ratios of quality of life indices and therefore accounts for not only health related costs, but non-health related costs(50). Drawbacks of CBA are related to the method of establishing monetary benefit and costs. Converting health outcomes into monetary values places a monetary value on human life and this is potentially ethically objectionable. Furthermore, not all benefits may be possible to convert into monetary values.

A net benefit analysis can often follow the analysis of cost benefit. The net benefit approach seeks to identify whether the net health benefit or net monetary benefit of one intervention compared against another is positive or not in order to ascertain which is preferable, essentially subtracting the costs of an intervention from its benefit to establish net benefit. This form of analysis is expressed in either monetary terms or in QALYs(26). Net health benefit is established by calculating the differences in quality of life while the net monetary benefit is established by calculating differences in costs.

4. Cost-Minimisation Analysis

Cost minimisation studies are generally undertaken when the benefits of health care have been found to be identical across the treatments being compared; for example, when a commercially available branded drug is compared to its identical generic version. Whilst a relatively simple form of economic evaluation, it is not common for health outcomes to be identical across treatment and strategy comparisons; there is consequently a burden of proof placed on the analyst to prove that this is indeed the case.

1.2.5 Perspectives in Economic Evaluation

The perspective taken in any health economic analysis is also of importance when considering the economic impact of the introduction of any new drug or therapeutic intervention. It has been argued that economic evaluation is pointless in the hospital setting as resources are simply moved elsewhere. However the increased productivity in

hospitals that occurs with the movement of resources derived after cost savings is reward in itself(51).

It is also argued that the perspective taken by economic evaluations should be as wide as possible to account for all benefits of treatment. Health economic studies that focus simply on health service costs ignore the secondary benefits of treatments to patients(52). For example, laser or surgical interventions in optic neuropathies may have the primary effect of protecting the visual function of the patient, but the secondary benefit of reducing the reliance of adherence to a treatment regimen of daily eye drops cannot be underestimated for the patient too. The gold standard in the UK in terms of perspective of an economic evaluation is the societal perspective, therefore the perspective taken is from those who use and pay for the NHS. An evaluation that focuses primarily on the perspective of the NHS may produce outcomes that ensure the most efficient service mix is provided to patients however it will not necessarily maximise society welfare. This occurs when sectors outside of healthcare are impacted as a result of health care interventions. Furthermore, a societal perspective also allows the analyst to get a true picture of opportunity cost implications of decision making, therefore understanding in greater detail the value of resources employed outside of the healthcare system(53).

1.2.6 Randomised Controlled Trials and Health Economic Modelling

Newly introduced treatments are best evaluated through randomised controlled trials (RCTs). RCTs are undertaken to establish the efficacy of medical interventions and to gain information on the possible side effects associated with them. RCTs typically randomises participants to receive one of two or more possible interventions. Participants are treated the same in all other respects in order to examine solely the differences that the intervention has upon the participant. Whilst RCTs are recognised as the gold standard in effectiveness analysis there are notable limitations associated with them. They are sometimes non-generalizable and considerably expensive to undertake given the amount of people involved within them and their duration(54). Beyond costs, the RCT may potentially be less medically relevant once reporting is complete due to advances in medicine that may occur over the time the RCT has taken to run. Ethical questions also may arise when RCTs are utilised in the testing of conditions with considerable reductions

in quality of life. RCTs often require one of their arms to be a control with no treatment, and when these trials are blinded, the subjects thinking they are receiving potentially effective interventions are actually not receiving any. This is specifically problematic in the case of irreversible medical conditions as non-treatment potentially harms the subject physiologically by withholding treatment.

Health Economic modelling can be used in conjunction or as an alternative to RCTs by providing information on the probability of cost effectiveness, potentially indicating the usefulness of the implementation of an RCT. Given their computerised nature, they provide a relatively inexpensive source of information for RCTs as they involve relatively few skilled professionals in their construction and processing. Whilst they are easier to undertake, like any modelling, they are restricted by the assumptions that underpin them however. They do still produce outcomes in a much more expedient fashion than with an RCT as the lead time from the initial planning stages to final data processing is usually around a year once full validation has been achieved(26). These models can also be adapted to address future research questions and used as a base for the economic evaluation of similar conditions that follow similar treatment pathways. Finally, and potentially most important, there are significantly fewer ethical concerns with health economic models compared to RCTs. As such, health economic models have grown in terms of implementation within health technology appraisals.

1.2.7 Types of Health Economic Modelling

Beck and Pauker (1983) introduced the application of the Markov models to derive patient outcomes whilst accounting for life expectancy(55). Markov models stratify patients to one if its constituent states, a state that reflects the subjects existing level of well-being. Members of each state can then move into other health states as a consequence of an event, the likelihood of which being modelled as a transition probability. Each state is designated a utility and the individual accumulates utility according to how long they remain a member of each state until the time horizon, the length of time the model is accounting for, has been completed. Costs are accounted for by establishing the unit cost of membership per state per cycle. This is then multiplied by how many members in the state, with costs being accumulated across the time horizon.

Most Markov models allow for multi-directional transitional movement, but in the case of irreversible disease patients can only move one way. The absorbing state such as death means no further movement can occur with no additional utility accumulated. It is also possible to model conditions perceived to be worse than death, such as those related to dementia and coma, and this is possible by attributing negative utility values to these health states. The Markovian assumption is an important characteristic of the Markov model and stipulates that events that take place in time periods prior to the cycle being modelled have no effect upon them. As such, all patients in a specified state will have a similar prognosis irrespective of their personal history unless complex Markov chains are derived, arguably a limitation of this method of modelling(55).

An alternative model structure to Markov models are the discrete event simulations (DES). A DES is relatively complex model that seeks to represent multiple interactions between individuals and clinical decisions. They are described as discrete event simulations as entities move forward from one event to another rather than in Markov cycles modelled within Markov models which move forward in time based phases. A DES is made up of patients that are provided with attributes, experience events and consume resources over time(56). The attributes can represent a multitude of patient characteristics that may influence the likelihood of an event whilst patient histories are also accounted for within the likelihood. Resource consumption can also be modelled on an individual basis within a DES. These type of models are especially relevant when the condition being mapped is event based and when there are multiple factors at play when decisions on treatment provision are made. There are limitations to the implementation of a DES however due to transparency issues around their reporting. They are often complex, limiting their interpretation and their adoption, especially within fields where the validation of outcome reporting is important.

1.2.8 Limitations of Health Economic Modelling

The difficulty associated with modelling treatment pathways linked to different conditions and the plurality of potential treatment modalities for them represents one particular limitation of health economic modelling. Furthermore, the definition of the parameters used in the model chosen also represents a significant challenge to the

analyst. Slight variation in parameters can lead to varying implications in terms of model interpretation, it is therefore important for the analyst to narrow the definition of parameters used as much as possible. These parameters are usually informed by existing medical research literature and there is often a lack in consensus when it comes to such research. This can often be due to slight variation in research methodology or sample populations. Therefore it is vital that medical research literature used to inform economic models are sourced from studies using the relevant research methodologies and relevant population demographics, a position supported by NICE(38).

In order to understand the limitations placed on health economic model outputs, measures of uncertainty known as sensitivity analysis are performed. Univariate sensitivity analysis seeks to quantify how variation in singular parameters affects the model's final output; it is a vital step in understanding uncertainty as it utilises the ranges around the parameters and re-simulates the model to produce alternative outputs(57). These outputs are then examined to see whether they surpass the chosen ceiling ratio against which cost-effectiveness is judged against. Deterministic univariate sensitivity analysis however seeks to identify the maximum limits of the parameter that can be tolerated before the health economic model moves into a non-cost-effective result. It therefore seeks to identity the cost-effective thresholds for the parameters utilised. Multivariate sensitivity analysis, otherwise known as probabilistic sensitivity analysis, establishes the distributions around which the models parameters can be explained and takes repeated samples from these distributions for each individual simulated patient. Once thousands of these patients have been simulated, CEPs can be plotted and the proportion of cost effective observations under specific ceiling ratios are calculated and plotted in cost-effectiveness acceptability curves(CEACs)(58). These CEACs provide a diagrammatic representation of the cumulative probability of acceptance according to varying willingness to pay.

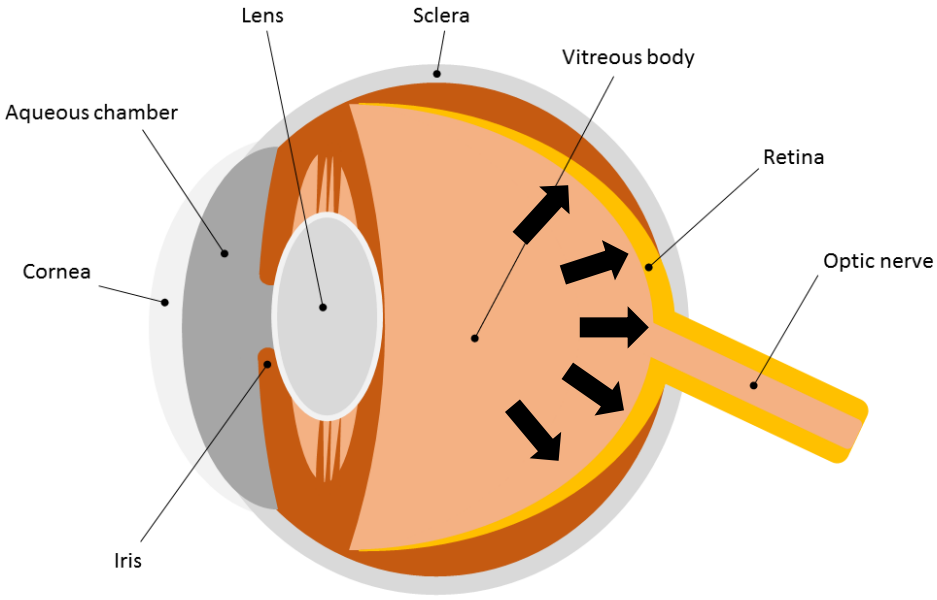
1.3 Glaucoma

1.3.1 Epidemiology of Glaucoma

Glaucoma is one of the most common causes of irreversible blindness in the world and has been projected to impact 79.6m people worldwide by 2020(59, 60). It is often termed

the “silent thief of sight” due to its long term and slow progressing nature and, as such, it is often not noticed until the person’s sight loss is advanced. Therefore, if left untreated, it can result in irreversible sight loss. The term “glaucoma” represents a group of irreversible progressive diseases thought to cause degeneration of the optic nerve due to damage of Retinal Ganglion Cells (RGCs)(61). Functional RGCs are essential to vision as they are responsible for collecting information from photoreceptors, transmitting it to the optic nerve which then transmits this information to the vision centres of the brain.

Figure 1-3: Schematic of the eye illustrating impact of raised intraocular pressure



There are subtypes of glaucoma each with their own specific characterisations. The most predominant form of glaucoma is primary open angle glaucoma (POAG) with around 2% of people over 40 years of age found to have POAG in the UK(62). One of the most significant risk factors for POAG is an elevated intraocular pressure (IOP) (see Figure 1-3). The pressure within the eye is usually regulated via management of aqueous fluid located within in the anterior chamber by its ‘drainage systems’. Reduction in aqueous outflow from the eye results in a build-up of pressure within the eye, resulting in optic nerve atrophy and, subsequently, damage of the subject’s visual field (VF). IOP is the only modifiable risk factor for glaucoma with detection usually centring upon elevated

pressures being observed, most commonly by opportunistic case detection, and managed through therapeutic intervention(63).

A further less common subtype of glaucoma is acute angle closure glaucoma (AAG) which occurs when there is a rapid increase in IOP caused by a sudden blockage to one of the eyes drainage systems located at the angle between the peripheral cornea and the peripheral iris(64). The trabecular meshwork within the angle which acts as a filter for the drained aqueous fluid therefore cannot allow for aqueous outflow, subsequently resulting in raised IOP. Whilst POAG is asymptomatic until damage is advanced enough to be visually perceived, AAG can cause sudden pain to the subject making it easier to detect and treat. Whilst both of these glaucomas are characterised by a raised IOP, it does not always result in damage to the optic nerve. This leads to a diagnosis of ocular hypertension (OHT), a potential precursor for glaucoma and occurs when high pressures are observed within the eye but without VF loss.

Optic nerve damage and VF deterioration can also occur in people with IOP values in the normal range, termed normal tension glaucoma (NTG). NTG has been suggested to have been attributed to fragile optics nerves susceptible to damage from normal IOPs or potentially by those who have previously had elevated pressure with optic nerve damage being halted once IOP has returned to normal levels(65). It has also been suggested that the optic nerve damage associated with NTG runs a course independent of factors related to IOP(66).

Optic nerve atrophy can also be caused by secondary glaucomas, so termed due to occurring as a side effect of other eye conditions with examples being exfoliative glaucoma, neovascular glaucoma and congenital glaucoma. Exfoliative glaucoma occurs due to blockage of the angle between the cornea and iris occurs caused by exfoliation of the lens(67), neovascular glaucoma occurs due to abnormal formation of blood vessels on the iris hindering the eye's drainage channels(68) whilst congenital glaucoma occurs in babies with inadequate drainage channel development(69). Secondary glaucomas are not common and represent the least prevalent form of glaucoma in the UK.

Existing literature has identified specific subgroups who are most likely to be at high risk of suffering from glaucoma. One of the primary risk factors for glaucoma is older age. Around 2 in every 100 people over 40 years of age are affected by POAG in the UK whilst this rises to around 5 in every 100 people over 80 years of age(70). It has been argued

this is due to the increased mitochondrial dysfunction observed in older age accelerating the loss of RGCs(71). Ethnicity has also been found to play a role in the onset of glaucoma. People of African or Afro-Caribbean ethnicity have been found to be at an increased risk of POAG compared to Asians and Europeans(72) whilst people of Asian origin have been found to be at increased risk of developing AAG(73). It is not currently known why people of African or Afro-Caribbean origin are at greater risk of POAG but the higher rate of AAG in Asian is attributed to their shallower anterior chambers compared to those of European decent(74). Family history is a further risk factor for glaucoma whilst those suffering from myopia and diabetes may also be at an increased risk(75-78).

1.3.2 Intraocular Pressure

IOP measurement has been historically the predominant method of assessing disease progression(79, 80). It is measured in terms of millimetres of mercury with 'normal' pressures shown to exist between 12-21 mm Hg and elevated pressures above that range. It is normally measured using a tonometer, an instrument that applies a small amount of pressure to the eye via a device or a short puff of air with the eyes IOP inferred from the force required to flatten an area of the cornea(81).

The use of IOP as a proxy measurement for monitoring the patient with glaucoma is not ideal. Glaucoma itself is a complex collection pathophysiological processes that combine many different components, of which IOP is one. Other 'structural' components need to be assessed like the central corneal thickness (CCT) and cup disc ratios (CDR) as a surrogate of optic nerve head health. Measurement of the thickness of the cornea is important as corneal thickness can interact with IOP measurements, potentially causing under or over treatment. Subjects with thin corneas (less than 555µm) tend to produce IOP measurements that are artificially low, potentially resulting in under treatment and progression to glaucoma(64). Subjects with thick corneas may indicate higher IOPs than is the case, potentially resulting inefficient treatment for a condition that the subject is unlikely to develop.

Assessment of the optic nerves, often clinically assessed as cup disc ratios, is important too. The optic disc represents the connected portion of the retina to the optic nerve and can either be flat or cupped in shape. Glaucoma detection depends on the measurement of the neuroretinal rim and the optic cup and their sizes relative to that of the optic

disc(82). As glaucoma progresses, the cup is observed to grow in size until it takes up the area of the optic disc. The cup disc ratio therefore compares the diameter of the cup of the optic disc to the diameter of the optic disc as a whole. A normal cup disc ratio is around 0.3-0.4 and ratios above this are potentially indicative of the presence of glaucoma. A high cup disc ratio is not necessarily an indication of glaucoma however; it is the change of ratio as the patient ages that provides evidence of its development. It is therefore difficult to diagnose glaucoma solely on the basis of optic nerve head analysis(83).

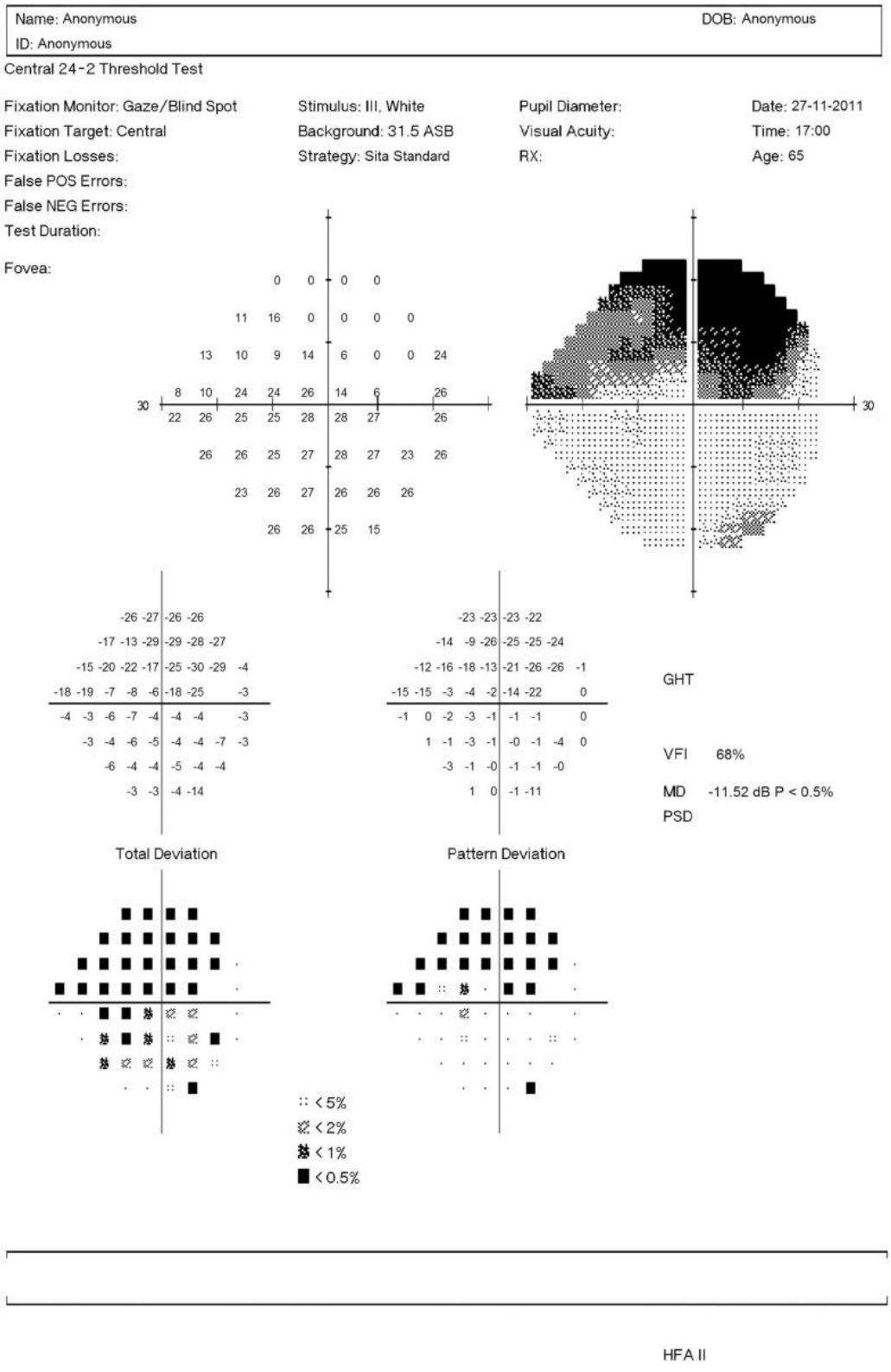
Whilst the monitoring of all these components represent key aspects of glaucoma management, it is important to make the link between physiological health and patient outcomes themselves. As such, clinical measurements for glaucoma management can be divided into either structural or functional measures. The former encompasses aforementioned components of IOP, CCT and CDR whilst the functional side seeks to measure the subjects' perceived vision. In the case of glaucoma, this is best estimated by the assessment of the VF.

1.3.3 Visual Fields

The visual field test can help detect defects in central and peripheral vision and is used in the diagnosis and management of glaucoma and its progression. The definition of the visual field is the area where light reaches the retina in the eye which in turn stimulates light perceiving cells located at the back of the eye. Ganglion cells process the information and transmit the data along their axons to the brain via electrical signals(84, 85).

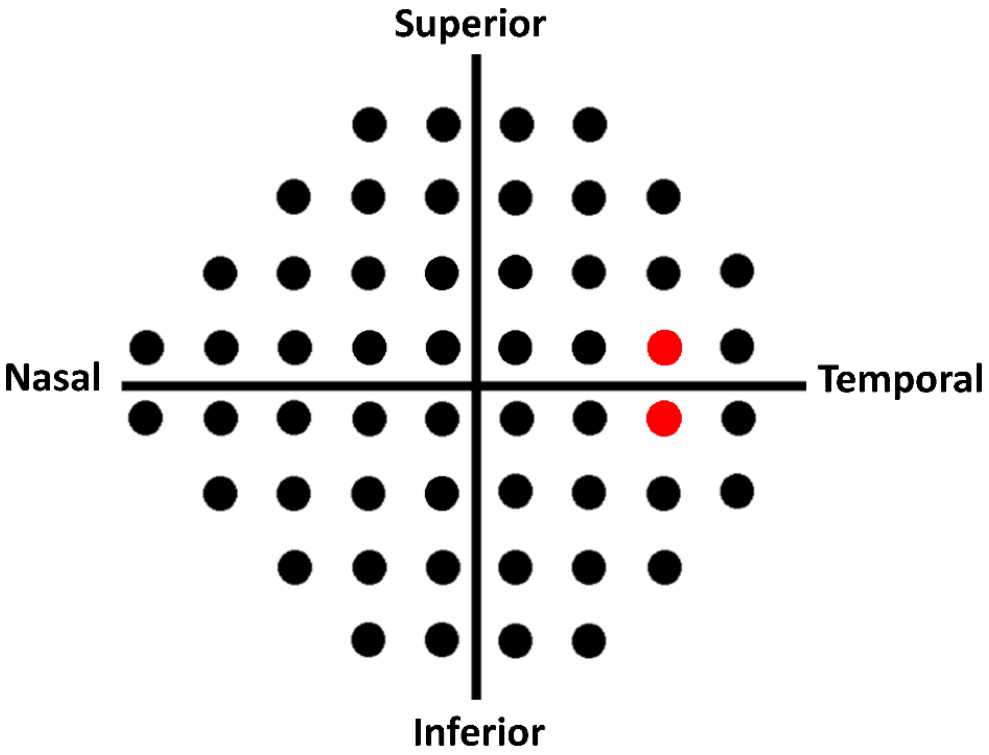
The visual field is normally assessed using perimetry whereby a person indicates when they detect the visual stimuli using one of their eyes whilst fixating, with the other eye being occluded. It can either be undertaken manually with the help of a clinical technician or automatically. Computerised automatic perimetry, ubiquitous in glaucoma clinics, is significantly more efficient than manual perimetry and automatically modifies characteristics of the stimuli in order to identify minimum detection threshold(86).

Figure 1-4: A HFA output indicating a visual field produced by a left eye. Fixation losses, false positives and false negatives are indicated in the top left.



It is undertaken using a "white on white" test referred to as standard automated perimetry (SAP) which assesses the subjects' light-difference sensitivity at different locations of the visual field (see Figure 1-4). The most common perimeters used are the Humphrey Field Analyzer (HFA) (Carl Zeiss Meditec Inc., USA) and the Octopus perimeter (Haag-Streit AG, Koeniz, Switzerland). This thesis will focus primarily on the outputs of the HFA as this instrument is the more commonly used in primary and secondary care eye clinics throughout the UK.

Figure 1-5: The 24-2 HFA testing grid for the right eye. Spacing of the points is 6° starting 3° from the centre. The red points indicate the blind spot



The HFA measures the visual field with different test patterns, the most commonly used clinically is the 24-2 grid; this tests the field to about 20 degrees (see Figure 1-5). 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 visually healthy person of a similar age (age-matched control). These location based data can then be expressed in terms of a global aggregation such as the mean deviation (MD), a measure which represents how

much the test subjects' visual field sensitivity deviates from age matched controls. Whilst the HFA provides a useful summation of the information on the subjects' visual field, it can potentially be misleading in the presence of cataracts within the eye being tested as an opaque lens can lead to excessive light scatter(64). The pattern deviation plot is useful in this situation because it corrects for an overall depression in light sensitivity. The glaucoma hemifield test (GHT) also adds to the information available to the analyst by providing an assessment of how glaucomatous the visual field appears to be. The GHT assesses the probability maps of the HFA to detect localised VF loss whilst also examining for symmetrical loss across the horizontal meridian and provides a simple classification of the VF based upon common patterns of glaucomatous loss(87-89) and has been reported to have high sensitivity and specificity(90). The GHT however is not designed to provide definitive glaucoma diagnosis and is instead recommend to verify clinical interpretation of the VF(64).

Perimetry is challenging for the patient and the VF results can be difficult to interpret. Perimetry is a psychophysical test and, simply put, relies on a person responding to a stimulus by pressing a button; the measurements are therefore not exact but are probabilities of reliably detecting a stimulus. One of the primary reasons for an unreliable visual field is the lack of perimetric experience in the subject undertaking the test and possible fatigue effects(91, 92). Learning effects occur when sensitivity increases during and between perimetric examinations whilst fatigue effects occur when sensitivity decreases during an examination(93, 94), Consequently, VF test outputs at the earliest stages of testing may prove unreliable. Therefore, in the follow-up of a patient, the first recorded visual field is typically excluded from further analysis (95, 96). Visual fields can also be excluded on the basis of the reliability criteria that is reported as part of the HFA visual field test. The HFA tests for fixation losses, false negatives and false positive errors as part of its testing algorithm(97), although the usefulness of these indices have been called into question(98, 99).

1.3.4 Quality of Life in glaucoma

Clinical measures of visual function do not necessarily provide information on how the patients' visual impairment may impact upon their quality of life. Visual field loss from glaucoma can impact upon the person's ability to read, drive and navigate obstacles(100, 101). The latter in particular can significantly impact upon the subjects as incidence of

falls have been found to be related to the degree of the patient's functional vision(102, 103).

Clinical assessment of visual function in glaucoma relies on monocular visual fields yet, obviously people function binocularly. Whilst the better monocular VF provides a useful indication of the patient's functional field of vision(104), a binocular VF provides a better representation of impairment faced by the glaucoma patient. The Esterman test is the one test for the binocular VF(105). The Esterman uses a set stimulus intensity of 10 dB over a 130^{o} horizontal field with 120 test points. Another approach combines existing monocular fields into one aligned binocular visual field: binocular summation and integrated visual field (IVF). Binocular summation can be undertaken by taking equivalent locations in both of the eyes and calculating the square root of the sum of the squares of those sensitivities(106). The IVF is also conducted by comparing corresponding locations in both of the eyes and simply takes the better of the two sensitivities to represent the binocular representation of the visual field in that location(107). It is not a perimetric test in itself and rather it compares existing monocular visual field tests, therefore negating the need for the subject to undertake further visual field examination. It has also been shown to correlate with the Esterman test(105), making it a valid method to retrospectively establish binocular visual function and has also been shown to produce similar results to the better eye MD(104).

The assessment of quality of life for glaucoma patients goes beyond the use of perimetric instrumentation and can be examined via the use of self-report questionnaires. Self-report questionnaires and patient reported outcome measures (PROMs) such as the EQ-5D in addition to patient interviews are becoming more frequently utilised as interest in patient orientated care expands. They are of growing interest as they give a direct representation as to how the patient themselves perceives the impact glaucoma has upon their quality of life(108). PROMs are sometimes used as end points in clinical trials but are not often used in the clinic but have been found to be popular for participants especially when the instrument is short, lending support to their utilisation within routine clinical practice(109). PROMs are, however, potentially limited when used within the context of visual impairment as individuals may feel they have an incentive to mask some of their responses in order to maximise their degree of care or to minimise the likelihood of having their driving license revoked(110). Furthermore, use of the EQ-5D in studies of

glaucoma and the impact of its treatment are limited as utility scores are argued to be related to MD in a nonlinear fashion(109).

In comparison to other chronic conditions, the relationship between glaucoma and quality of life has not been explored in significant depth(111). The focus of research on quality of life in glaucoma patients however has centred upon its impact on fitness to drive and the ability to perform daily activities. Studies have found that those with advanced glaucoma are more likely to experience a motor vehicle collision than those with healthy vision(112). Legislation in the UK regarding fitness to drive specifies a minimum visual acuity of at least 6/12 (0.5 decimal) with both eyes open. Furthermore, significant binocular VF loss such as homonymous or bitemporal defects which come close to fixation, as measured by the Esterman test, indicates that the subject is no longer legally fit to drive(113). Studies have also found that glaucoma impacts upon the subjects ability to read with those with bilateral defects having a slower reading speed(114). Furthermore it has also been shown that glaucoma patients struggle with reaching and grasping objects(115), balance(116) and navigation(117, 118).

1.3.5 NICE Guidelines on Glaucoma

Guidelines were produced for the NHS in the UK by NICE for the treatment of those with or suspected of having glaucoma to establish clinical monitoring and treatment pathways(62). In order for the patient to make informed decisions, the guidelines state that patients should be supplied with relevant and accessible information pertaining to the pathophysiology of the condition, the patient's existing health state and the possible lifelong implications of the disease. The guidelines also specify that the patient should be made aware that glaucoma is asymptomatic in its earliest stages and that all glaucomatous VF damage is irreversible, in addition to information on the role family history plays in the development of the disease.

Guidelines on glaucoma further state that potential treatment pathways should be explained and detailed to the patient whilst describing the importance of patient compliance in the effective treatment of the disease(1). Information and support with registration and certification of visual impairment should also be provided, including details regarding contacting the Driver and Vehicle Licensing Agency (DVLA) about their condition.

Once the individual has been diagnosed with or is suspected of having glaucoma, baseline VF measurements for analysis are required. IOP measurement using Goldman applanation tonometry (GAT) should also be undertaken alongside the analysis of Central Corneal Thickness (CCT), gonioscopy to assess the depths of the anterior chamber and VF testing. Optic nerve head images should also be recorded in order to maximise the information available in the classification of disease status.

Table 1-1: NICE Guidelines on COAG Monitoring Intervals

		Patient Monitoring Intervals (Months)	
IOP at Target	**Progression**	**IOP only**	**IOP, Optic Nerve Head, VF**
Yes	No	n/a	6-12
Yes	Yes	1-4	2-6
Yes	Uncertain	n/a	2-6
No	No	1-4	6-12
No	Yes	1-2	2-6
No	Uncertain	1-2	2-6

Source: NICE Guidelines: CG85 **(62)**

Following identification of disease, long term monitoring of IOP fluctuation, the optic nerve head and the VF is required (see Table 1-1). Progressing patients should have their IOP, optic nerve head and VF measured at 2-6 month intervals whilst those not progressing are recommended to undergo full testing every 6-12 months. Those with an uncertain definition regarding progression status should be monitored at 2-6 month intervals irrespective of whether IOP is at target or not.

Guidelines on IOP monitoring alone vary according to IOP control, with those achieving target not recommended to undergo further testing unless progression is identified (1-4 month intervals). Patients not achieving target IOP control are recommended to be monitored every 1-2 months if there is any suspicion of progression or 1-4 months if not.

Treatments offered to the patient, as with monitoring, vary according to the risk of the individual progressing to a state of visual impairment. Those newly diagnosed with early to moderate COAG and at risk of visual impairment in their lifetime should be offered

pharmacological treatment depending on comorbidities and drug interactions. Those with severe COAG and at risk of further visual impairment in their lifetime should be offered surgical intervention in conjunction with pharmacological treatment. The information and benefits that are associated with surgery should also be provided to the patient in order to allow them to state their preference in terms of the treatment they receive.

1.3.6 Treatment Modalities

Treatment for glaucoma centres on the reduction in IOP because it is the only modifiable risk factor for disease progression. There are three main categories of interventions: pharmacological, laser and surgical. Pharmacological intervention often represents the first line of treatment for glaucoma and usually takes the form of self-administered eye drops; these seek to improve the drainage of the aqueous fluid in the eye or by the decreasing the production of the aqueous fluid, thereby reducing the amount of pressure in the eye. They are classed in terms of their active ingredient which can include prostaglandin analogues (PGAs), beta blockers, alpha agonists or carbonic anhydrase inhibitors (CAIs)(64). The different pharmacological agents are prescribed depending on how the side effect profile impacts upon the glaucoma patient. Prostaglandin analogues such as Latanoprost work by enhancing uveoscleral outflow whilst also being noted to have some effect upon the trabecular meshwork and has recently been shown to reduce IOP levels by 4 mm Hg in treatment naïve patients(119). Beta blockers such as Betaxolol work by decreasing the production of aqueous fluid in the eye whilst Alpha agonists such as Brimonidine work by both decreasing the production of aqueous fluid and by increasing its drainage. Carbonic anhydrase inhibitors also work by reducing the production of aqueous fluid and are available both in forms of eye drops (Dorzolamide) or pills (Acetazolamide).

Pharmacological agents are limited due to patient non-adherence to treatment and this occurs for a variety of reasons. Patients have reported difficulty in directing the bottle over the eye appropriately resulting in missed drops, difficulty in squeezing the bottle and the inability to read bottle labels or to identify the bottle(120, 121). Patients have also reported issues remembering to administer the drops themselves whilst some have reported lack of belief in the eye drop regime impacting on their condition(122, 123).

Laser treatment (laser trabeculoplasties) tend to be one off procedures and suffers less from the issues relating to adherence. Laser is also occasionally used as the first line of treatment for glaucoma in those requiring more aggressive treatment for their glaucoma and those unable to adhere or tolerate the side effects of the pharmacological agents. Laser trabeculoplasty utilises high energy light beams in order to unblock the trabecular meshwork within the eye to increase aqueous outflow, therefore reducing IOP. They are usually relative quick to perform and, given the use of anaesthetic, painless. They are not a permanent solution however and the patient sometimes requires repeat procedures to prolong IOP management. There are two forms of laser trabeculoplasty: argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT). Of the two, ALT was the first to be developed with SLT developed in more recent years given issues associated with ALT regarding long term efficacy and attrition(124).

The final line of treatment for glaucoma and therefore the most aggressive intervention is a surgical filtration intervention referred to as a trabeculectomy. With the patient placed under anaesthetic, part of the trabecular meshwork and adjacent structures are removed in order to improve the outflow of aqueous fluid in the eye. Fluid is subsequently drained into a “bleb” that is covered by the conjunctiva, consequently lowering eye pressure(64). Alternative forms of surgical intervention options are available such as a deep sclerectomy operations which implants a device inside of the eye to increase drainage whilst aqueous shunts implants tubing to drain aqueous fluid from the eye(125, 126). These forms of interventions tend to be the most invasive and expensive and, as such, are not prescribed to glaucoma patients unless an aggressive approach to treatment is required or if the other forms of interventions have failed(127).

Treatment choices are complicated however due to the imperfect nature of the information available to the clinician. At the point of diagnosis, the clinician will have access to information regarding the patient’s IOP, CDR and existing level of VF damage amongst other factors, but there is a further level of information required in order to ensure allocatively efficient resource allocation: rate of glaucomatous VF progression. Those progressing at the fastest rates represent those who are most likely to have a negative impact upon their quality of life and as such represent the cohort that resources should be targeted at. Identifying these patients however requires considerable time and resources in itself, leading to growing discussion into whether we should be intensifying

monitoring at the earliest stage of glaucoma identification to reduce the long term economic burden of the condition by identifying these patients sooner(15, 128).

1.3.7 The Role of visual fields in the Clinical Management of Glaucoma

Whilst individual VFs are used to inform the clinician on the existing level of damage to the patient, VFs collected in series can provide information on the rate of deterioration of functional vision. Therapeutic decisions can therefore be based upon risk to patient quality of life in their residual lifetime given existing damage and progression rates. Accurate rate identification however requires a considerable length of VF series due to the variability associated with perimetry and risk factors alone cannot accurately indicate who will progress fast or slowly(129). Whilst a large proportion of patients progress slowly, a small but significant proportion of patients progress at rates that could quickly lead to visual disability. It is therefore important to understand each patient's rate of progression in order to individualise treatment and to tailor it to their risk of progression to visual impairment(89).

Frequency of monitoring of the VF usually depends on the severity of glaucoma and the age of the patient. Stable glaucoma patients are usually monitored every 6 to 12 months whilst progressive and advanced glaucoma being monitored every 2 to 4 months(64). The European Glaucoma Society (EGS) however has issued guidelines that recommend that the VF should be tested 6 times in the first two years in order to better identify those progressing rapidly(128), with the World Glaucoma Association echoing this sentiment(130). Such an intensified regime of follow up has been argued to be sufficient to detect fast progression with annual follow up being adequate following this intensified follow up period(15). Clinicians can therefore better target resources towards these fast progressors, increasing glaucoma service delivery efficiency by expediting access to more aggressive treatments to those most of risk of quality of life reductions, therefore reducing the economic burden of glaucoma.

1.3.8 Economic Burden of Glaucoma

Given its irreversible chronic nature, glaucoma consumes considerable clinical resources throughout the patient's lifetime, therefore warranting further economic

evaluation(131). Studies have sought to quantify the burden of visual impairment and glaucoma has on healthcare systems worldwide. In the US, Lee and colleagues(132) examined the direct resource consumption associated with glaucoma at varying severities They found that ophthalmology-related resource use increases with glaucoma severity, with costs ranging from $623 to $2511 per year for glaucoma suspects and end stage glaucoma respectively. This finding has been supported by other studies(133, 134). These studies also suggested delay of disease progression to visual impairment would reduce the economic burden and should be of interest to policy makers.

Beyond direct costs of visual impairment, significant indirect costs have been observed. In a study of age related macular degeneration, Meads et al. sought to examine and quantify the costs averted by treatment for the prevention of progression to visual impairment in the UK(135). A detailed top down study of the main cost factors relating to age related macular degeneration (AMD) was performed. Costs of blindness from the perspective of the NHS and other local and national government agencies in the first and following years were estimated. Resources relating to low vision clinics, low vision rehabilitation, acute hospital admissions resulting from injuries caused by low vision in addition to residential and community resource consumption. Cost ranges for the first year of blindness were estimated between £1375 and £17100 with the following years of blindness estimated at between £1325 and £16800 per year.

Further expanding on the work of Meads et al., Lafuma and colleagues undertook an estimation of the total non-medical costs associated with visual impairment in France, Italy, Germany and the UK(136). Local prevalence rates of visual impairment were established along with estimates for the rates of non-registered visually impaired persons. Unit costs were sourced from national databases and from the manufacturers directly whilst healthcare professionals were interviewed to establish treatment durations. Total annual costs (per individual) were estimated at €10.749bn (£8.4bn) for France, €9.214bn (£12.7bn) for Germany, €12.069bn (£11.7bn) for Italy and €15.18bn (£13.7bn) for the UK. The main cost components of visual impairment in the community were loss of income (23-43%), burden on carer (24-39%) and paid assistance (13-29%). A significant proportion of economic consequences of visual impairment were concluded to lie beyond direct health costs, especially once effect on productivity has been accounted for. Payers must therefore take into account non-medical social costs in order to truly understand the economic consequences of visual impairment. Beyond the costs

faced by the payers, significant non-medical costs of glaucoma to the patient have been found. In a study of costs faced by glaucoma patients attending hospital based clinics, Sharma et al found the maximum mean cost per visit of £16.20 and a minimum mean cost of £12.90 with travel found to represent one-fifth of the total patient costs(137).

There has also been study of the strategic management of glaucoma in order to increase the cost-effectiveness of glaucoma management, therefore reducing the economic burden of the disease. Following the release of NICEs guidance on glaucoma, there has been growing calls for referral refinement schemes to be put in place in local communities to reduce the amount of false positives associated with glaucoma detection(138-140). Sharma et al. studied the costs of running a community based care model whereby community optometrists were provided with training and accreditation in glaucoma. These optometrists were then able to run half day clinics in their own practices whilst also being available to assist in their local hospitals. The study found that the cost per attendance in the community clinic to be more than double that of hospital clinic attendance although the costs to the patients were marginally cheaper with the community clinic. These higher costs were explained by extra overheads tied to localised service provision, illustrating the complex nature of resource consumption associated with glaucoma and the NHS.

Given the increasing direct and indirect resource burden, important decisions regarding the amount of resources that should be invested into optimal progression detection are required. Decisions need to be made as to whether the investment in progression reduction yields acceptable improvements in quality of life relative to non-investment. A key tool available to health care payers that helps inform the investment decision process is cost-effectiveness evaluation.

1.4 Objectives of the Thesis

1.4.1 Chapter 2

Several HE studies have been carried out on competing treatments for glaucoma(141-144), but the health economics of monitoring the condition in secondary care has received little attention. Monitoring and management of glaucoma patients in the UK cause considerable direct costs and, in England and Wales alone, it has been estimated

that there are more than one million glaucoma related outpatient visits in the hospital eye service annually(62). In addition to these direct costs, considerable indirect costs, to both the patient and caregivers, are also incurred (135, 145). Significant trends between the costs of glaucoma and the severity of disease have also been observed in the UK, Europe and the USA(133, 134). As such, there is a potential economic argument for earlier detection and better monitoring of glaucoma in order to reduce both the number of patients progressing to sight loss and the long-term economic burden of disease(15).

The measurements from VF testing are notoriously variable which necessitates frequent monitoring and/or a long period of time to precisely detect true disease progression. There is sound evidence, from retrospective studies and statistical modelling that increasing the frequency of VF testing (more examinations per year) leads to earlier detection of progression(15, 146-149). An adequate number of VF tests must therefore be performed over a given period in order to separate true disease progression from the measurement variability inherent in VF data. This idea of more frequent monitoring however presents a dilemma for service delivery for patients with COAG: if VF changes are not detected early enough, because of infrequent testing, there may be long term costs associated with disease progression following inadequate treatment; conversely if patients are examined too often there is increased pressure on clinical resources.

Whilst research recommendations by Chauhan et al (2008), adopted by the European Glaucoma Society, suggest that three VFs in each of the first two years of follow-up are necessary to detect 'fast' VF progression in newly-diagnosed glaucoma patients(15, 128), the economic consequences relative to the utility however has not been evaluated, and as such requires exposition. The best way to examine any new proposed monitoring scheme would be with a randomised clinical trial. No such study has been performed and it would have to be substantial and thus costly. A health economic model was therefore constructed using different monitoring intervals to detect VF progression rates in all newly-diagnosed COAG patients to examine the cost effectiveness of increased VF testing. Two different VF monitoring schemes were defined as current practice (annual VF testing) and proposed practice (three VF tests per year in the first two years after diagnosis) and examined. It is hypothesised that proposed practice applied to some groups of patients will yield improved clinical information and therefore increase the cost-effectiveness of clinical care. The outcome of this economic evaluation could potentially provide information to assist decision-makers allocating of scarce resources

so that benefits can be maximised, or inform the design of an appropriate prospective study.

1.4.2 Chapter 3

The work reported in Chapter 3 seeks to examine the parameters used in the health economic model. This chapter aimed to investigate how the severity of glaucoma at the point of detection is changing over time, specifically represented in the health economic model as the existing health state parameter. The identified methods can then be used to update the HE model whilst the finding will also be of interest to those stakeholders interested in case detection of glaucoma. Late presentation with an advanced stage of disease is a significant risk factor for long term adverse outcomes and better knowledge of the number of patients that fall into this category could be useful for clinicians (150, 151). Population screening for glaucoma has been proven to not be cost effective given existing levels of prevalence and there is currently no existing glaucoma detection strategy in the UK with identification currently reliant upon opportunistic case finding(63).

More detailed interrogation of the large-scale electronic records from routine clinical practice that were used to initially formulate the existing health state parameter in the health economic model was consequently undertaken. The long-term trends were then identified to test the hypothesis that the degree of vision loss at diagnosis had improved over time.

1.4.3 Chapter 4

The work reported in Chapter 4 also seeks to examine the parameters implemented within the health economic model, investigating how rates of glaucoma progression are changing over time. The identified methods can then be used to update the HE model whilst it is also of research interest to stakeholders to examine the trends associated with rates of glaucomatous VF loss over time. New topical treatments for glaucoma and OHT have been introduced since the turn of the millennium and it is still not clear whether the introduction of these interventions have resulted in a reduction in disease progression(152).

The study of large scale records routinely collected in clinics across England provides an opportunity to assess the real world outcome of treatment whilst also monitoring trends in health service delivery of glaucoma. This chapter therefore sought to test the hypothesis that rates of glaucomatous VF loss are improving over time whilst also seeking to more accurately describe the distribution of VF rates being observed in England by patient age and disease severity. Importantly, the work described in this chapter also considers the frequency of visual field testing that is currently carried out in glaucoma secondary care.

1.4.4 Chapter 5

The work in Chapter 5 updates the health economic model by incorporating the findings reported in Chapters 3 and 4. These re-simulations were undertaken to increase the confidence around the ICER that was derived. Also, costs of visual impairment were also added to the model in order to incorporate the societal costs of visual impairment into the analysis. It is relevant to consider the impact that such costs have upon the cost effectiveness of increased early stage glaucoma monitoring as, by reducing the proportion of those who progress to a state of visual impairment, such costs can be averted. Deterministic and probabilistic sensitivity analysis of the new ICERS were also undertaken to examine the degree of confidence surrounding the re-simulated models outputs.

1.4.5 Chapter 6:

Chapter 6 presents future work in the pipeline following the conclusion of the studies described in the previous chapters of the thesis. In order to fully comprehend priority in health service delivery, it is important to measure how patients perceive their condition. It has been argued that the quantification of patient utility represents an area that requires further research as it focuses specifically on the impact disease has upon patient wellbeing(111). This is especially the case in glaucoma as a significant proportion of those with the condition do not progress to a state of visual impairment(153).

As an extension of the work being undertaken in this thesis, a study of patient perception of glaucoma is currently being set-up to study the impact of glaucoma diagnosis. It has

been suggested that the diagnosis of a disease can have greater impact on the patient's quality of life than the disease has itself(154, 155). To examine the impact of patient diagnosis, a bespoke questionnaire comprising of the Brief Illness Perception Questionnaire (Brief IPQ), EuroQol 5D (EQ-5D) and the Type D Personality Scale (DS-14) was constructed to test the null hypothesis that there is no difference between mean Brief IPQ score for the cases and the controls.

The questionnaire has been presented to patients at Bedford Hospital NHS Trust and Hinchingbrooke Hospital with cases identified as those newly diagnosed with glaucoma or OHT and controls representing matched existing patients. These matches are performed in terms of patient age and existing disease severity measured by visual acuity and HFA outputs. Personality variation is also being controlled for using the DS-14 in order to make sure the respondents general outlook on life doesn't impact upon the study findings. This chapter also discusses other potential future work resulting from the findings in this thesis.

Chapter 2: Health economic modelling and evaluation of different monitoring intervals in glaucoma patients

The work reported in this chapter formed Chapter 5 of a National Institute for Health Research (NIHR) report called, "Frequency of visual field testing when monitoring patients newly diagnosed with glaucoma: mixed methods and modelling"(1); see List of Supporting Publications. For that chapter, Trishal Boodhna authored the entire health economic model, performed the data analysis and also led the write up of the chapter. The other significant contributors to this piece of work were Richard Russell (who helped with the writing and some of the analysis) and David Crabb who conceived the idea of the study and supervised it. Rodolfo Hernández (University of Aberdeen) assisted with some of the ideas underpinning the health economic model and commented on a draft of the work. Ananth Viswanathan and Rizwan Malik provided clinical advice on the health economic model.

2.1 Introduction

As discussed in the introduction to this thesis, glaucoma, as a chronic condition, requires care and management for life. Careful clinical follow-up is required in order to assess stability of the disease and to provide the appropriate level of treatment and, as such, the monitoring and management of the disease represents a significant economic burden to the NHS. Statistical modelling has highlighted the potential benefits of performing 3 VF tests in each of the first two years of glaucoma follow-up in order to detect 'fast' progression of VF loss in newly diagnosed glaucoma patients(128). However, the economic consequences relative to the utility that would derive from such a strategy have not been evaluated.

This chapter describes a study that examined the cost-effectiveness of existing practice (annual testing) compared with the recommended practice of 6 VF tests in the first two

years in the newly diagnosed patient. The benefit of moving to such a strategy is that clinicians would have earlier access to the subject's rate of VF loss instead of relying on risk factors for progression; something that is currently not possible with any certainty(156, 157). By accounting for the rate of progression, clinicians can ultimately better target services for those individuals most likely to move into a state of visual impairment in their lifetime(15, 158, 159), improving the productivity of services rendered by the NHS.

In order to examine the cost-effectiveness of extra VF testing at glaucoma identification, a health economic model was constructed to examine the ratio of extra costs relative to improvements in quality of life. These were then compared against the NICEs willingness to pay ceiling ratio for every extra QALY derived in order to ascertain whether the proposed practice was cost-effective for the NHS. In order to specify the health economic model, a detailed exploration of the literature pertaining to the costs, effects and management of glaucoma was undertaken to inform the parameters that represent the foundation of the model. Examination of existing health economic models used in glaucoma were also studied in order to help identify the structure of health economic model that best applied to the condition.

2.2 Literature Review

2.2.1 Costs of Glaucoma

In terms of the direct costs of glaucoma, Traverso and colleagues examined resource utilisation in glaucoma and consequently established its economic impact in a multicentre study across Europe(134). When direct costs for the examined patients were identified across 6 universally accepted states of glaucoma, a statistically significant upward linear trend was observed with disease worsening (P=0.018). With each increment, costs increased by €86, starting from €455 at stage 0 to €969 at stage 4, with medication costs totalling 42% to 56% of total costs across all stages. This lead the authors to conclude that the effective delay of VF progression would significantly constrain the economic burden of glaucoma, a finding supported by further costing studies undertaken within ophthalmology(135, 136).

Beyond the direct costs of visual impairment, significant indirect costs have also been observed. Meads et al. sought to examine and quantify the costs averted by treatment for the prevention of progression to visual impairment in the UK(135). A detailed top down study of the main cost factors relating to AMD was performed. Costs of blindness from the perspective of the NHS and other local and national government agencies in the first and following years were estimated. Resources relating to low vision clinics, low vision rehabilitation, acute hospital admissions resulting from injuries caused by low vision in addition to residential and community resource consumption. Cost ranges for the first year of blindness was estimated between £1375 and £17100 with the following years of blindness estimated at between £1325 and £16800 per year with the highest costs being observed to be related to residential care.

2.2.2 Utility Quantification in Glaucoma

Kobelt et al.(160) undertook a study of the relationship between glaucomatous VF loss and patient quality of life using 199 patients responding to a bespoke questionnaire. The authors observed that progression from mild glaucoma to severe glaucoma resulted in a decrease in utility from 0.84 to 0.72 respectively. These differences were not statistically significant however until progression to the most severe stages of disease. When better eyes was examined against worst eyes, it was found that the better eye had improved correlation with quality of life whilst worst eye MD only had mild correlation. These results led the authors to conclude that there was a link between visual function and quality of life that was especially notable in those with the most severe forms of VF loss.

In another study of glaucoma and quality of life, Burr et al.(161) measured utility by developing the Glaucoma Utility Index. Using focus group studies a new multi-dimensional tool was developed incorporating central and near vision, lighting and glare, mobility, daily activities and eye discomfort amongst other factors. A scale of difficulty was then assigned to each dimension and a discrete choice experiment was used to develop a preference based utility measure. The greatest impact on respondents was found when moving from a state of perfect health to severe disability in central and near vision, resulting in in the most significant loss of utility in respondents with daily living and mobility the next biggest factors. Subsequently, utility scores of 0.8015, 0.7471, 0.7133 and 0.5350 were derived to represent mild, moderate and severe glaucoma and visual impairment, defined using the Bascom Palmer staging system(162).

2.2.3 Treatment and Visual Function

In the Canadian Glaucoma Study, Chauhan et al.(75) evaluated the impact of IOP reduction on rates of VF loss. 216 patients were followed at 4-month intervals; patients underwent VF testing at each visit and progression was analysed. Gender and mean follow up were not linked with MD rates but increasing age was associated with a worse MD rate. In terms of IOP and field change at the first endpoint in the analysis, an IOP reduction of 3.1mm Hg/year was associated with a change in MD rate equal to 0.25dB/year whilst an IOP reduction of 3.0mm Hg/year corresponded to a change in MD rate equal to 0.24dB/year at the second endpoint. Consequently, the authors concluded that a relatively small reduction in IOP resulted in significant improvements to the rate of VF progression.

In a similar study of IOP and the VF, Folgar et al(163) sought to establish the efficacy of surgery in reducing VF progression by conducting a retrospective analysis of patients with repeatable VF loss. Those enrolled underwent successful glaucoma surgery in either eye with at least 2 years of follow-up before and after the surgery. 28 eyes of 28 patients were enrolled with the mean number of VFs per patient equal to 13.4 spanning 7.1 years on average. Mean IOP was found to decrease from 19.0mm Hg to 11.3mm Hg following surgery, while mean global progression rates fell from -1.48 dB/year to -0.43 dB/year. Thus, a 1mm Hg reduction in IOP resulted in approximately a 0.1 dB/year increase (improvement) in global rates of progression. For a typical patient, surgical intervention would therefore impede progression to blindness by 19 years. The authors concluded that reduction in IOP levels caused by successful surgical intervention has a significant impact upon the glaucomatous VF progression.

2.2.4 Health Economic Modelling of Glaucoma

Burr et al. built a health economic model to compare opportunistic case finding to two proposed screening strategies to assess whether screening met the UK National Screening Committee (NSC) criteria(63). Opportunistic identification by community based optometrists was considered current practice, against which, a technician-based screening strategy, and a glaucoma specialist optometrist screening strategy, were compared. Markov modelling was then utilised to simulate how these different strategies would impact upon patients and resource use. The authors found that general population

screening was not cost-effective at the given prevalence rate and that screening would need to be targeted at specific subgroups aligned with the established risk factors in order for it to be considered cost-effective. However, the estimated low prevalence rate suggests that, even with targeted screening, cost-effectiveness may still not be achieved based upon a usual threshold value of around £30,000 per QALY gained(47). Prevalence was found to be a principal factor of cost-effectiveness; with a screening interval of 10 years, a rate of around 3% to 4% in a 40-year-old cohort would be required for the strategies to be cost-effective. Perspective was also found to be an important element of analysis as when societal impact was accounted for, a prevalence of just 1% was deemed cost-effective. Less important parameters affecting cost-effectiveness were progression rates and utility values associated with each health state. Thus, it was concluded that COAG screening in the UK met with the NSC criteria for treatment but not for screening.

More recently, van Gestel et al reported on the construction and validation of a Discrete Event Simulation (DES) health economic model, with sufficient transparency, using an existing model of ocular hypertension and glaucoma extended to account for decisions on treatment and effects(164). Utility was linked to the patient's stage of glaucoma and costs were associated to the level of treatment undertaken. The model underwent stringent tests of internal and external validity, face validity was also achieved through interdisciplinary meetings analysing the input parameters. Credible health economic outputs could be derived after 30 minutes of computation per cohort. There were significant advantages identified with DES models, especially in the case of complex and diverse treatment modalities such as glaucoma; however, the authors noted that further work is required to increase the transparency of such models in terms of structure and outcomes as these are likely to cause difficulties in outcome reporting.

2.3 Methods

2.3.1 The Model

A Markov model was constructed to model the proposed practice of increased VF monitoring frequency against existing practice. The Markov model was chosen because of its relative simplicity and relative transparency in comparison with other models (i.e. discrete event simulations). All the programming for the model was implemented in Excel (Microsoft Excel 2010; Microsoft Corporation, Redmond, WA, USA). Markov models

'stratify' patients to be always a member of one of its constituent Markov states, a state that reflects the subject's existing level of well-being. The members of each state can then move into other health states dependent on the transition probability. Each Markov state is designated a utility weight and the individual accumulates utility according to how long he or she remains a member of each state. The model is run for a length of time (e.g. 25 years) known as the 'model time horizon'. This time horizon is broken down into equal parts, denoted as Markov cycles (e.g. 1-year intervals). In addition, all Markov models have at least one absorbing state in which all individuals will eventually enter if the model is given a sufficiently long time horizon.

Figure 2-1: The structure of the Markov Model for glaucoma. Patients can only transition to the next state in sequential order, remain in the same state or be classified as deceased at each Markov cycle.

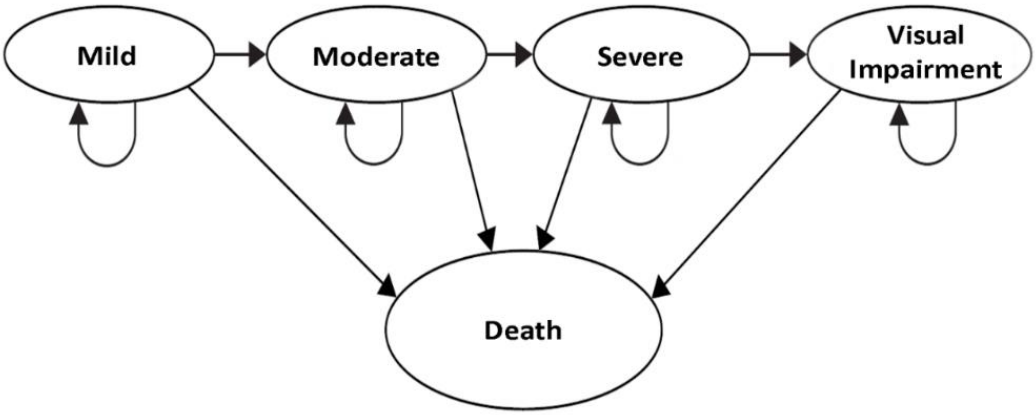


Figure 2-1 presents a schematic representation of the Markov model constructed in this study. This Markov model seeks to represent how glaucomatous visual field progression manifests within the patient and how it is treated in real world clinical settings. It should be noted that this model focuses solely on those with a diagnosis of COAG, it therefore is not representative of the treatment pathways that OHT patients may experience. Furthermore, measurable damage to the patient's VF is used to represent the progression the disease and its severity over time. The disease in this model therefore progresses over time according to the rate of MD deterioration with this progression being controlled by treatment which lowers the patient IOP. By lowering the patient's IOP, we in turn lower the rate of progression and the probability of the patient progressing to worse disease severities. As such, the model seeks to evaluate the cost-effectiveness of

gaining expedited access to information on patient progression rate in the proposed practice so as to increase the amount and level of treatment the faster progressors receive. Model parameters were sourced from Medisoft VF databases (Medisoft Ltd., Leeds, UK) containing 473 252 VFs from 88 954 patients were downloaded in 2012 from glaucoma clinics at Moorfields Eye Hospital in London, Cheltenham General Hospital Gloucestershire Eye Unit, Queen Alexandra Hospital in Portsmouth and the Calderdale and Huddersfield NHS Foundation Trust. These databases were interrogated and analysed to provide data on patient initial health states and progression rates in addition to patient demographic distributions and how these initial damage and progression rates varied by these demographics.

The Markov states in Figure 2-1 represent, from left to right, increasing disease severity. Individuals can start in any of these states according to the state of their disease at diagnosis. In a particular model cycle, patients can remain within their existing state of health, or progress towards increased disease severity. Most Markov models would allow for multidirectional transitional movement, but in the case of an irreversible disease, such as glaucoma, a unidirectional movement (towards a worse disease severity) is the only transition possible. In addition, it is assumed that patients move sequentially and cannot skip states because of the relatively slow evolution of the disease and the yearly defined cycle lengths defined in the model. Patients may also leave the model and move into the absorbing state (death).

Chauhan et al. supported the idea that performing three VF tests in each of the first two years of follow-up is helpful in detecting 'fast' progression of VF loss in newly diagnosed glaucoma patients(15). Identification of these patients is hampered by the large variability of VF test results over time, and thus it was suggested that at least six VF tests are required in the first two years to identify those progressing rapidly (at a power of 80%). Two different strategies, defined as current practice (annual VF testing) and proposed practice (three VF tests per year in the first two years after diagnosis), were consequently modelled. The specific hypothesis was constrained to investigating if the proposed practice was more cost-effective than current practice. In short, this study seeks the benefit of getting more precise information of progression earlier by using proposed practice. This gain in information, especially in identifying rapidly progressing patients sooner, is hypothesised to yield improved cost-effectiveness of clinical care.

Table 2-1: Intervention years by strategy

Strategy	Rate of progression	VFs Required	Improved information intervention year
Current practice	Stable	13	14
	Slow	13	14
	Medium	6	7
	Fast	5	6
Proposed practice	Stable	15	12
	Slow	15	12
	Medium	8	5
	Fast	7	4

Table 2-1 shows how intervention points varied by strategy in this model. Current practice was specified such that fast progressors (defined as those patients in whom VF MD worsens by –1.5 dB/year) would be identified after five VF tests, medium progressors (defined as –1 dB/year) identified after six VF tests, and slow progressors (defined as –0.25 dB/year) or patients defined as stable identified after 13 VF tests, that is a significant ($p < 0.05$) slope would be identified by linear regression of MD after these time periods. These intervention points are based on research by Chauhan et al.(15) however their model was further developed to account for duration of follow-up, as described by Alm(165). Like the Chauhan et al. research, simulations were based on a rate of progression of MD with statistical power equal to at least 80% and moderate variability (SD of MD measurements equal to 1). The results of the simulations indicated that proposed practice (six VF tests in the first two years, followed by one VF test per year) identifies fast progressors by the fourth year of monitoring, medium progressors by the fifth year, and slow and stable progressors by the 12th year, with at least 80% power.

2.3.2 Treatment Pathways

To model the decision-making process behind treatment allocation and its impact on the probability of transition to worse states of disease, ophthalmologists with a specialist interest in glaucoma on the project management group (hereafter referred to as 'the clinical review panel') were consulted to construct simplified treatment pathways that

patients would face in a UK NHS tertiary setting. It was concluded that, at the initial stages of treatment, decisions on treatment allocation are largely informed by the patient's risk of progression (informed by IOP, central corneal thickness, optic nerve head and other clinical assessment), their existing level of damage and their age. Thus, treatment pathways were specified to depend on a variable that denoted to be progression risk, existing VF damage and the patient's age. In short, those classified as a high priority were more likely to undergo surgical-based treatment strategy, whereas those categorised as a low priority were more likely to undergo a pharmacologically based treatment strategy.

In order to model the effects of treatment on the probability of transition to a more severe state, the proportional relationship between IOP reduction and rate of MD progression identified by Folgar et al.(163) was used; consequently, a 1 mmHg reduction in IOP translated to a 0.1 dB/year improvement in MD rate. In terms of the treatments, three lines of therapy were defined: first-line therapy was stated as a pharmacological-based regimen; second line as the patient undergoing argon laser trabeculoplasty (ALT) treatment alongside topical medication; and third line as surgery (i.e. trabeculectomy). Based on the recommendations of the clinical review panel, it was assumed that patients would be provided with pharmacotherapy from the point of identification as a glaucoma suspect; therefore, this level of treatment wasn't modelled to have any further reduction on progression rate and probability of transition.

Table 2-2: Decision Nodes for Treatment Lines given Imperfect Information

	High Risk		**Low Risk**	
Health State	**50 y/o**	**70 y/o**	**50 y/o**	**70 y/o**
1	2	1	1	1
2	2	1	1	1
3	3	2	2	1
4	3	3	3	2

Source: Clinical review panel

To map how patients filter through the model into different treatment modalities, treatment pathways were identified and constructed based on NICE guidelines and expertise from the clinical review panel. Hypothetical subjects were assigned and

categorised according to characteristics based on age, risk of COAG progression, existing level of damage and rate of progression, resulting in 48 distinct patient groupings and pathways in the economic model. Within a time period described as 'imperfect information', where the managing clinician is 'unaware' of the patient's rate of progression of glaucomatous VF damage, the clinical review panel was asked to grade the level of treatment that would be provided to the patient given his or her age, existing level of damage and risk of COAG conversion (see Table 2-2). A high and low risk stratification is used to represent probability of the patient progressing to a state of visual disability within their residual lifetime based upon structural measurement of the eye. This factor therefore seeks to represent those at high risk of progression based upon structural measurements such as cup disc ratios and central corneal thickness. It was deemed important by the clinical review panel to account for structural measurements in the assessment of treatment modality decision making, therefore a high risk low risk dichotomy reflecting the clinical review panels assumptions on structural distribution was incorporated into the model. After a defined number of VF tests, the patient's progression rate is identified and then the model moves into a time period defined as 'perfect information' (see Table 2-3). The clinician now had the opportunity to continue to provide the patient with the existing degree of treatment, or to increase it.

Tables 2-3a and 2-3b detail the interaction between decision nodes utilised in the economic model given 'perfect information'. For example, a 50-year-old patient entering into glaucoma care at health state 1 (mild damage) and defined as being low risk of progression would receive the first line of treatment. If the patient was subsequently defined as a 'fast progressor', he or she would be moved on to third-line treatment as a result of the increased risk of moving into a state of visual impairment in his or her lifetime. This functionality was built into the model to reflect the resource reallocation that occurs once the clinician identifies those patients who are potentially undertreated. This temporal improvement in patient management is what underpins this study, as the more expedient allocation of efficient treatment modalities differentiates the proposed practice of increased VF monitoring from what is presently carried out in clinical practice.

Table 2-3: Decision Nodes for Treatment Lines given Perfect Information and a) high patient risk of progression b) low patient risk of progression

a)

	Stable		Slow		Medium		Fast	
Health state	**50**	**70 y/o**	**50 y/o**	**70 y/o**	**50 y/o**	**70 y/o**	**50 y/o**	**70 y/o**
1	2	1	2	1	3	2	3	3
2	2	1	2	1	3	2	3	3
3	3	2	3	2	3	3	3	3
4	3	3	3	3	3	3	3	3

Source: Clinical review panel

b)

	Stable		Slow		Medium		Fast	
Health state	**50 y/o**	**70 y/o**	**50 y/o**	**70 y/o**	**50 y/o**	**70 y/o**	**50 y/o**	**70 y/o**
1	1	1	1	1	3	2	3	3
2	1	1	1	1	3	2	3	3
3	2	1	2	1	3	2	3	3
4	3	2	3	2	3	3	3	3

Source: clinical review panel

2.3.3 State Transition Probabilities

The probability of transition from one state to another was defined as a function of the patient's rate of progression and his or her existing level of damage. Following the methodology suggested by Hernández et al., the transition probability was calculated by first establishing the cohort mean level of damage then establishing the level of further damage required in order for a member of the cohort to move into the next health state. The years to threshold was established by dividing the change required to reach the threshold of the next state by the progression rate of the cohort. Finally, the transition probability was identified following the methods of Briggs et al.(26), dividing 1 by the amount of years to the threshold.

Intrinsic to the model is how patients move across health states and progress from a mild disease severity to visual impairment. The key driver for this model is the individual's progression rate; patients within the Medisoft databases are stratified by age group and whether they are stable, slow, medium or fast progressors. For patients in the younger

cohort, it was observed that 49.2%, 36.4%, 12.2% and 2.3% were characterised as stable, slow, medium and fast progressors respectively with 33.8%, 41.0%, 21.0% and 4.2% observed in the older cohort (see Table 2-6). These results are supported by the Canadian Glaucoma Study, which showed that increasing age was associated with a faster MD worsening rate(75).

Once the patient has received a specified number of VF tests, and depending on the patient's underlying rate of progression, a period defined as 'perfect information' starts. The patient's rate of progression is now measured with sufficient accuracy to inform and adjust treatment allocation. At this stage, the patient is allocated resources efficiently, depending on the risk of reaching visual impairment within their lifetime.

2.3.3 The Effectiveness of Treatment

Table 2-4: Review of studies examining the effectiveness of laser (second line) and surgical (third line) intervention

Modality	Source	Start IOP	End IOP	IOP Reduction	MD Reduction
Laser/ 2nd Line	Melamed (2003)	25.5	18.5	7.0	-0.70
	Heijl (2002)	20.6	15.5	5.1	-0.51
	McIlraith (2005)	26.0	17.7	8.3	-0.83
	GLT (1995)	27.2	17.7	9.5	-0.95
	Juzych (2004)	24.3	17.0	7.3	-0.73
				Average	***-0.74***
Surgery/ 3rd Line	El-Sayyad (2000)	28.2	14.1	14.1	-1.41
	Kobayashi (2003)	24.8	12.6	12.2	-1.22
	Wilson (2003)	26.9	13.2	13.7	-1.37
	Beckers (2003)	22.3	12.6	9.7	-0.97
	Folgar (2010)	19.0	11.3	7.7	-1.05
	Gedde (2007)	25.6	12.7	12.9	-1.29
				Average	***-1.22***

To quantify the effectiveness of the treatment, a review of literature detailing the improvements in IOP associated with the treatments was performed. For studies where IOP change rather than MD progression rate changes were reported, the proportional relationship between IOP reduction and rate of MD progression identified by Folgar et al.(163) was used with a 1 mmHg reduction in IOP being translated to a 0.1 dB/year improvement in MD rate. Mean improvement in MD rate following ALT (second-line treatment) was equal to 0.74 dB/year whilst literature on surgical intervention (trabeculectomy) suggests it offers a mean improvement in MD rate of 1.22 dB/year (see Table 2-4). Transition probabilities were therefore adjusted for cases where second and third line levels of treatment were prescribed in accordance with the decision nodes specified by the clinical review panel.

2.3.4 Patient Demographics

Table 2-5: The modified Bascom Palmer glaucoma staging system

Severity	**Range**
Mild	0 dB to -6 dB
Moderate	-6 dB to -12 dB
Severe	-12 dB to -20 dB
Visually Impaired	Worse than -20 dB

Source: Bascom Palmer glaucoma staging system(162)

Health states were defined according to a modified Bascom Palmer glaucoma staging system(162) because of its use of MD and to facilitate data synthesis from studies also using this staging system (see Table 2-5). This staging system identifies mild glaucomatous VF defects as those with a MD between 0 dB and –6 dB, moderate VF defects as those with a MD between –6 dB and –12 dB and severe VF defects as those with a MD between –12 dB and –20 dB; patients with worse MDs are classified as visually impaired. These levels of damage were required to exist in the patient's better eye (the eye with the larger/healthier MD) rather than their worse eye, since research suggests that the level of VF damage in a patient's better eye has a closer relationship with functional vision and utility estimates relative to that of the worse eye(166-169). Patients were, therefore, allocated to health states based on baseline disease severity.

Table 2-6: Population parameters for the health economic model

Parameter	Subgroup	Stratification	Input
Population demographics	Gender	Male	52.90%
		Female	47.10%
	Age	50 years	28.15%
		70 years	71.85%
	COAG risk	High	20.00%
		Low	80.00%
Progression rate distributions	50 years	Stable	49.15%
		Slow	36.36%
		Medium	12.16%
		Fast	2.33%
	70 years	Stable	33.82%
		Slow	41.00%
		Medium	20.97%
		Fast	4.22%
Health state distributions	50 years	Mild	65.00%
		Moderate	21.40%
		Severe	9.96%
		Visually Impaired	3.65%
	70 years	Mild	66.20%
		Moderate	20.90%
		Severe	9.25%
		Visually Impaired	3.72%
Initial mean damage	50 years	Mild	-3.08dB
		Moderate	-8.32dB
		Severe	-15.50dB
		Visually Impaired	-23.98dB
	70 years	Mild	-3.11dB
		Moderate	-8.42dB
		Severe	-15.38dB
		Visually Impaired	-23.64dB

Source: Crabb et al. (1)

A retrospective multicentre study of VF databases (Medisoft) in the UK was performed to provide baseline population parameters for the Markov model (1). Findings suggested that the distributions observed could be represented as two clusters with mean ages of 51.2 years (28%) and 70.2 years (72%); therefore, for simplicity, patients within the model were set to enter the analysis at either the age of 50 or 70 years in the proportions given (see Table 2-6).

The ages at which patients are specified to enter are important, as returns on investments are dependent on the residual life expectancy of those being invested in; the longer the residual life expectancy, the greater the return of investment in terms of QALYs derived and years of visual impairment avoided. The ages chosen were also required to dichotomise younger patients and older patients with sufficient differential as decision nodes within the model also vary by age group. As a result of the clustering analysis, four separate cohorts were identified for individual cohort analysis within the model, in addition to an analysis of all cohorts (termed full simulation).

Patients within the model were dichotomised by gender and by age characterisation analysing separate cohorts of males aged 50 and 70 years (M50 and M70 cohorts, respectively) and females aged 50 and 70 years (F50 and F70 cohorts respectively). The results of the full simulation and the M70 cohort were of most interest, as the full simulation represents all patients within the UK glaucoma service, while the M70 cohort represents the group of patients least likely to provide cost-effective results, given they have the lowest residual life expectancies of all cohorts modelled.

In modelling existing damage at first presentation for the younger cohort, 65.0% of patients were specified as having mild glaucoma, 21.4% were defined as having moderate glaucoma, 10.0% were specified as having severe glaucoma and 3.7% of patients defined as visually impaired. In the older cohort, these figures were very similar, 66.2%, 20.9%, 9.3% and 3.7% respectively. The mean level of existing VF damage for the younger cohort was –3.08 dB, –8.32 dB, –15.50 dB and –23.98 dB for the mild, moderate, severe and visually impaired subgroups, respectively, while these figures were –3.11, –8.42, –15.38 and –23.64, respectively, for the older cohort.

2.3.5 Costs and Utilities within the Model

The costs of treatment were derived from Traverso et al.(134) as the treatment patterns modelled by the authors were similar to those in the current study and the glaucoma staging system was identical; thus, facilitating the resource costs calculation associated with each health state. In seeking to study how glaucomatous disease severity interacted with resources consumed, the authors established costs for various stratified disease stages. As the analysis models only three possible lines of treatment, resource consumption was analysed within the findings of Traverso et al. Thus, the treatment pathway identified by the authors for 'mild glaucoma' was specified as the first line of treatment, the pathway identified for 'moderate glaucoma' was specified as the second line of treatment and the pathway identified for 'severe glaucoma' was specified as the third line of treatment. These pathways were chosen as they bore the closest semblance to the three pathways specified in this economic model. Consequently, patients in the second line of treatment were costed to undergo a trabeculoplasty every 12.3 years (an average of two times over the 25-year time horizon utilised in this model), while those in the third line of treatment were costed to undergo a trabeculectomy every 11.2 years. Table 2-7 indicates that additional consumption of medications and alternative treatments within lines of treatment were possible. For example, those in the second line of treatment are costed to undergo a trabeculectomy every 37.0 years; however, given the starting ages of the cohorts and the 25-year time horizon used, trabeculectomy is a relatively small cost in this treatment line.

Table 2-7: Resource consumption by the three lines of treatment employed

	Treatment Line		
Resource	**First**	**Second**	**Third**
Cost	£777.47	£875.47	£1083.23
Office visits (per year)	3.0	3.1	3.7
Visual fields (per year)	1.4	1.5	1.6
Medications (per year)	14.4	20.4	21.6
Trabeculoplasties (per 100 years)	3.5	8.1	5.3
Trabeculectomies (per 100 years)	2.5	2.7	8.9

Sources: Traverso (2005)

A key driver of the cost-effectiveness of proposed practice is the cost of supplemental VF tests. In the main, these represent a short-term investment which may help clinicians to provide the appropriate level of service provision in the long term. For the health economic model, these extra VF tests were specified to be performed by technicians and costs, sourced from the National Schedule of Reference Costs (2010–11) were found to be £56.54 per additional test undertaken(170).

2.3.5 Utilities within the Model

Table 2-8: Utilities associated with the different health states used in the model

Disease severity	Utility Score
Mild	0.8015
Moderate	0.7471
Severe	0.7133
Visually Impaired	0.5350

Source: Burr (2007)

The utility weights associated with each health state were derived from Burr et al.(161). This glaucoma study was selected as it was based in the UK and, therefore, of direct relevance to the model presented here, a requirement of NICE(38). Participants were asked to select one choice out of 32 discrete choice sets to indicate preferences in addition to completing EQ-5D questionnaires and visual analogue scales (VASs). They were then objectively graded according to their binocular VFs using the integrated VF (IVF) method described by Crabb et al.(171). Analysis then followed using regression techniques to establish utility weights for each disease dimension, resulting in health state utility scores (see Table 2-8). As such, mild, moderate, severe and visual impairment stages were represented by scores of 0.8015, 0.7471, 0.7133 and 0.5350 respectively.

2.3.7 Discounting

The cost and QALYs associated with future treatment were discounted as costs and benefits accrued in the future are valued less than they are today due to the short-term

inter-temporal time preference of rational economic agents. Thus, costs and utilities were discounted at a rate of 3.5% per year, as specified by NICE(38).

2.3.8 Model Validation

To ensure that the model reflected clinical management in a rational manner, internal and external model validation was undertaken. Internal validation was performed by varying the parameters used in the model and analysing whether or not expected and rational outputs were derived. The model was then adapted or corrected based on the outcomes of these variations relative to assumptions. External validation was achieved by supplying the clinical review panel with access to the model in order to establish whether or not modelled pathways were representative of that observed within clinical contexts. Feedback was also provided as to whether or not the model generated rational outputs when parameters were altered within rational limits.

2.3.9 Base case Analysis

The economic evaluation was modelled in full (including all cohorts of glaucoma patients; 'full simulation') and then stratified by each cohort to analyse how subgroups individually impacted model findings. Primarily, this analysis focuses on the findings of the full simulation and that of the M70 cohort, as this specific cohort represents the least cost-effective cohort within the analysis (given the lower residual life expectancies based on their gender and starting age). The main outcome of interest was the incremental cost-effectiveness ratio (ICER), representing the costs per QALY derived by proposed practice. ICERs were established by identifying the ratio of the changes in costs incurred to the QALYs achieved between current practice and the proposed strategy. The analysis was conducted from the perspective of the UK NHS, while costs were expressed in pound sterling. The cost and derived QALYs associated with future treatment were discounted at a rate of 3.5% per year, as specified by NICE(38) as costs and benefits accrued in the future are valued less than costs and benefits accrued today.

2.3.10 Sensitivity Analysis

Table 2-9: Baseline parameters ranges used in tornado diagram modelling

Description	Parameter	Baseline	Low	High
Cost	First Line	£777.47	£388.74	£1,166.21
	Second Line	£875.47	£437.74	£1,313.21
	Third Line	£1,083.23	£541.62	£1,624.85
Health State	Health state 1	0.8015	0.7471	0.9720
	Health state 2	0.7471	0.7133	0.8015
	Health state 3	0.7133	0.5350	0.7471
	Health state 4	0.535	0.2700	0.7133
50-year-old progression rate distribution	Stable	49.15%	24.58%	73.73%
	Slow	36.36%	18.18%	54.54%
	Medium	12.16%	6.08%	18.24%
	Fast	2.33%	1.17%	3.50%
70-year-old progression rate distribution	Stable	33.82%	16.91%	50.73%
	Slow	41.00%	20.50%	61.50%
	Medium	20.97%	10.49%	31.46%
	Fast	4.22%	2.11%	6.33%
50-year-old disease severity distribution	Mild	65.00%	32.50%	97.50%
	Moderate	21.40%	10.70%	32.10%
	Severe	9.96%	4.98%	14.94%
	Visually Impaired	3.65%	1.83%	5.48%
70-year-old disease severity distribution	Mild	66.20%	33.10%	99.30%
	Moderate	20.90%	10.45%	31.35%
	Severe	9.25%	4.63%	13.88%
	Visually Impaired	3.72%	1.86%	5.58%
Treatment effect	First Line	0.00	0.00	0.00
	Second Line	-0.74	-0.51	-0.95
	Third Line	-1.22	-0.97	-1.41
Risk of COAG	High	20.00%	10.0%	30.0%
	Low	80.00%	70.0%	90.0%
Discount rate		3.50%	1.75%	5.25%
Implementation Cost		£0.00	-£1,000.00	£1,000.00

One-way sensitivity analysis was undertaken in order to identify which parameters are most important on outcomes from the economic model using maximum and minimum model assumptions with results being displayed as tornado diagrams. Tornado diagrams utilise the maximal and minimal assumptions of each parameter to create a maximum and minimum derived ICER, the ratio between changes in costs and changes in effects, with differentials charted in order of magnitude (largest differentials are located at the top and the lowest at the bottom), creating the shape of a tornado.

Table 2-9 indicates the limits for the health economic model's parameters examined in the tornado analysis. Discount rate, costs and progression rates were all varied by 50% in order to set maximum and minimum limits. Utility was limited such that maximum and minimum limits were set to baseline assumptions of the parameters above and below the specific health state. Treatment effects were limited to the maximum and minimum observations for MD change associated with the modality identified in the review of literature, while risk distributions were varied by 10% in either direction. Further DSA, investigating the impact of marginal variations in parameters, was then performed focusing on the most important parameters that had been identified in the tornado diagrams. One-way analysis was then undertaken to investigate the impact caused by variation in individual parameters on ICERs identified.

Table 2-10: Parameter distributions for probabilistic sensitivity analysis

Description	Parameter	Mean	Distribution	Alpha	Beta
Utility	Health state 1	0.8015	Beta	37.94	9.4
	Health state 2	0.7471	Beta	278.07	94.13
	Health state 3	0.7133	Beta	49.11	19.74
	Health state 4	0.535	Beta	9.87	8.58
Costs	First line	£777.47	Gamma	15.37	50.6
	Second line	£875.47	Gamma	15.37	56.98
	Third line	£1,083.23	Gamma	15.37	70.5
	Implementation	£410,000	Gamma	9.09	45,093.55
Treatment effects	First line	0.00 dB	n/a	n/a	n/a
	Second line	–0.74 dB	Gamma	19.56	0.04
	Third line	–1.22 dB	Gamma	46.14	0.03

n/a, not applicable.

The model's parameters were also examined using PSA (Table 2-10). Simulations were performed 10,000 times in this study, with incremental QALY gains, incremental costs and the resultant costs per QALY associated with each simulation recorded. Once simulated, ICERs were calculated and plotted on the incremental cost-effectiveness plane (CEP). From these, cost-effectiveness acceptability curves (CEACs) were formulated indicating the probability of proposed practice being accepted at given levels of willingness to pay.

A combination of the PSA and the DSA was performed in order to further examine the relationships between important parameters in the model and the probability of acceptance of proposed practice at a given willingness to pay. VF test costs, discount rates, risk distributions and costs of visual impairment were all selected to be analysed in combination with the PSA. The cost of performing individual VF tests was varied to gauge its impact on probabilistic cost-effectiveness; cost was varied from £38.76 (lowest estimation) to £70.45 (highest estimation) following the maximum and minimum assumptions of the National Schedule of Reference Costs (2010–11)(170).

Discount rates were also varied to see how time preferences may impact on the health economic model's findings. Time preference was varied between a low discount factor of 0% (future costs and patient utility valued the same as they would be in the present) and a high discount factor of 5% (future costs and utility valued less than they would be in the present). The proportion of patients defined within the model as presenting with a high and low risk of progression was also varied in order to analyse how this parameter impacted on probabilistic cost-effectiveness. An initial division of 80% and 20% in low- and high-risk categories, respectively, was analysed within the model following consultations with the clinical review panel. In the PSA, these risk specifications were varied to 90% and 10% and to 70% and 30%, for the low- and high-risk patient groups respectively.

Finally, as the economic model was performed from the perspective of the UK NHS, thus not accounting for the costs to society of patients progressing to visual impairment, analysis of the impact that a change in perspective may have on outcomes was introduced, with costs of patients being defined as visually impaired incorporated. Per annum costs to society of £250, £500, £750, £1000 and £1758.50 (the threshold where costs of visual impairment cause proposed practice to derive a lower total cost than

current practice, therefore dominating it) for each patient defined as visually impaired were, therefore, introduced.

2.4 Results

2.4.1 Base case analysis

Table 2-11: Summary of results for all cohorts studied and the full simulation

		Current Practice		Proposed Practice		Incremental		
Cohort	**Age**	**Average Costs**	**Average QALYs**	**Average Costs**	**Average QALYs**	**Costs**	**QALYs**	**ICER**
M	50	£12,903	10.97	£13,204	10.98	£301	0.02	£17,655
	70	£5,339	4.25	£5,627	4.26	£288	0.01	£26,531
F	50	£13,289	11.33	£13,590	11.35	£301	0.02	£17,013
	70	£6,065	4.91	£6,358	4.92	£293	0.01	£21,924
Full Sim		£7,765	6.41	£8,059	6.43	294	0.01	£21,679

In total, 10,000 patients entered into the model under the full simulation while 3801 patients entered into the model under the M70 cohort. Under the full simulation, a positive cost differential of £294 per patient was identified between proposed practice and current practice (see Table 2-11), unsurprisingly implying that higher costs were associated with proposed practice. A positive utility differential of 0.01 QALYs per patient was also identified, implying greater utility associated with proposed practice. Thus, an ICER of £21,679 was derived for proposed practice, a figure within the hypothetical NICE ceiling ratio of £30,000. For the M70 cohort, incremental costs per patient and incremental utility per patient were £288 and 0.011 respectively.

The resulting ICER was thus equal to £26,531 per QALY, a ratio higher than that derived from the full simulation owing to the lower residual life expectancies of patients in the cohort. Findings were reflected in the F70 cohort with per patient cost and utility differentials of £293 and 0.013 QALYs, respectively, and an ICER equal to £21,923. Outcomes for the M50 and F50 cohorts were lower than that of the full simulation, as the residual life expectancies analysed for these cohorts were lower. Incremental costs

per patient were equal to £301, incremental utility per patient equalled 0.017 QALYs and 0.018 QALYs and ICERs equalled £17,655 per QALY and £17,013 per QALY, for the M50 and F50 cohorts respectively. Of the 10,000 patients who entered into the model under the full simulation, a total of 834.65 visual impairment-years were saved with proposed practice (see Table 2-12), equating to £3,517 per year of visual impairment saved. In the M70 cohort, this number was 229.18 years saved for proposed practice, while, in the M50, F50 and F70 cohorts, 173.97, 162.91 and 268.58 years were saved respectively.

Table 2-12: Years of visual impairment saved with the proposed practice relative to current practice

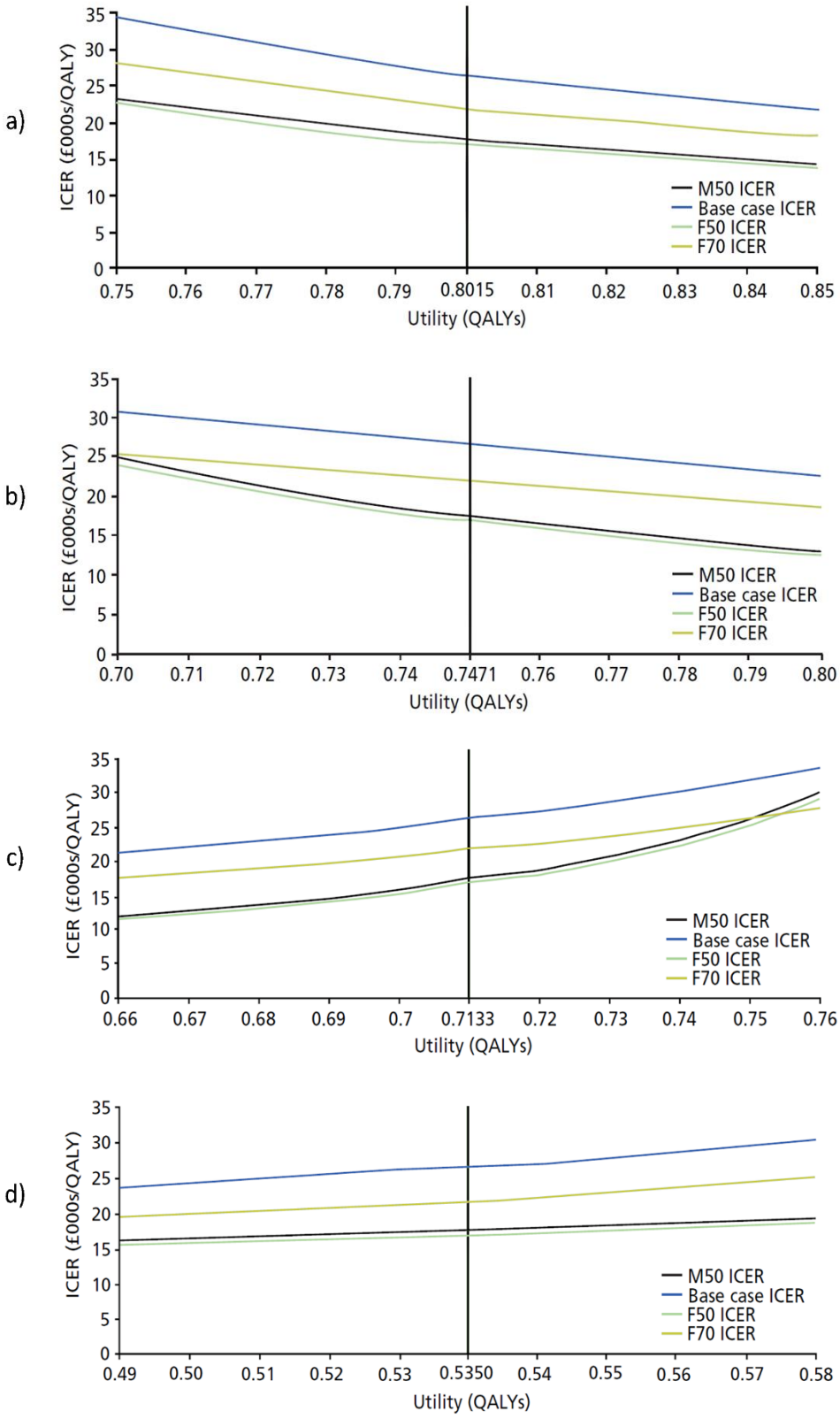
Cohort	Subgroup	Visual Impairment Years saved
M	50	173.97
	70	229.18
F	50	162.91
	70	268.58
Total		834.65

2.4.2 Deterministic Sensitivity Analysis: One way analyses

One-way analyses verified that the M70 cohort was the least cost-effective subgroup for all parameters examined, while the F50 cohort the most cost-effective cohort; this result is expected given the differences in each cohort's residual life expectancies and, therefore, the ability to recoup investment. In addition, the results for the M50 and F50 cohorts were closer than those observed between other combinations of cohorts owing to the similarities between these cohorts' residual life expectancies.

The utilities associated with health state membership were varied in 0.01 QALY increments from baselines of 0.8015, 0.7471, 0.7133 and 0.5350 for utility health states 1, 2, 3 and 4, respectively, with ICER impacts assessed (Figure 2-2). A negative relationship between the parameters and ICERs was observed for the utility associated with health state 1 for all cohorts, although only a decrease in utility in the M70 cohort was found to push ICERs above £30,000 per QALY. Similar findings were observed for the utility associated with health state 2; however, a reduction in this utility caused an accelerated increase in ICERs for the M50 and F50 cohorts compared with the 70-year-old cohorts.

Figure 2-2: One-way analysis of utility health states. (a) Utility health state 1, baseline = 0.8015 QALYs; (b) utility health state 2, baseline = 0.7471 QALYs; (c) utility health state 3, baseline = 0.7133 QALYs; and (d) utility health state 4, baseline = 0.5350 QALYs.



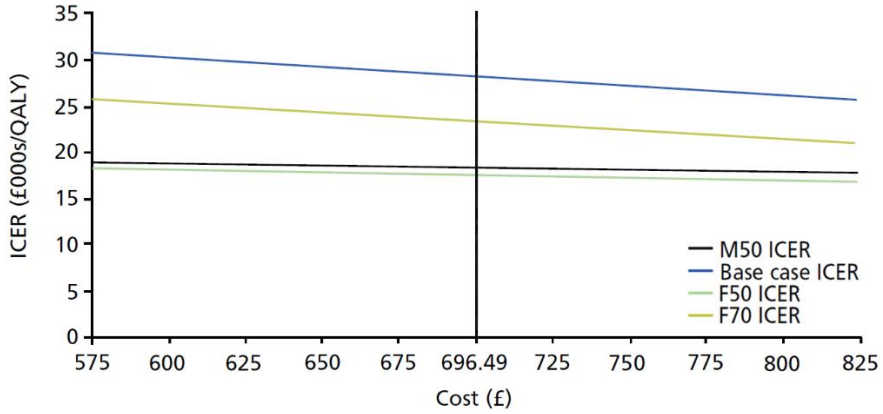
When the utilities of health states 3 and 4 were examined, a positive relationship existed between parameters and cohort ICERs. Within utility health state 3, the M70 and M50 cohorts surpassed the £30,000 per QALY ratio when utilities were increased; however, only the M70 cohort tipped this ratio when the utility of health state 4 was examined.

Treatment costs were varied by increments and decrements of £25, in the range ± £125 from a baseline of £696.49, £784.28 and £970.40 for first-, second- and third-line treatment costs, respectively (Figure 2-3). For first-line treatment costs, a negative relationship was observed between this parameter and ICERs of all cohorts, but the M70 cohort was the only grouping to surpass the £30,000 per QALY mark when treatment costs were reduced to £600. For second-line treatment costs, a positive relationship was found in the M70 and F70 cohorts, while a marginal negative relationship was observed in the M50 and F50 cohorts; however, the £30,000 per QALY mark was not exceeded in any cohort. For third-line treatment costs, a slight positive relationship was observed within all cohorts; however, the £30,000 per QALY mark was not surpassed for any cohort. The nature of these relationships can be attributed to the fact that proposed practice and current practice utilises the different treatment lines to varying extents across the patient characteristic framework (for example, proposed practice implements first line treatment to a lesser degree than current practice as it identifies fast progressors sooner. Thus, these patients receive more aggressive treatments lines earlier).

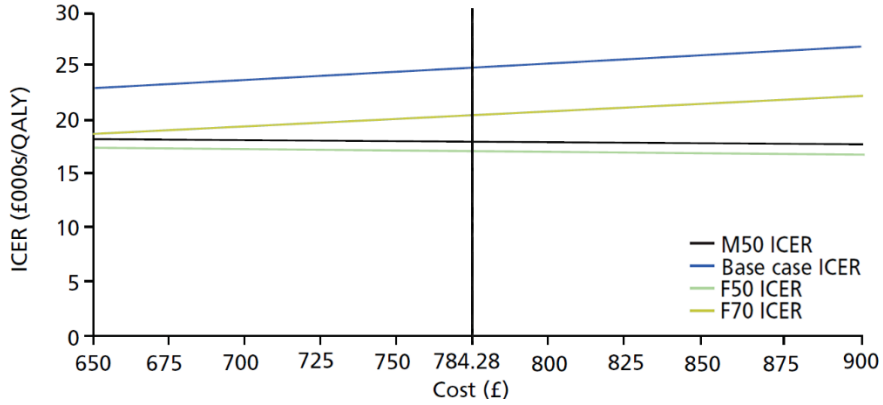
First-line treatment effects on rate of VF progression were analysed in 0.05 dB/year decrements from 0 to –0.5 dB/year from a baseline of 0 dB/year, –0.74 dB/year and –1.22 dB/year for first-, second- and third-line treatment costs, respectively (Figure 2-4). It is worth noting here, again, that an improvement in treatment effects is associated with a decrease in the rate of MD progression. The second- and third-line treatment effects were varied in increments or decrements of 0.05 dB/year and the impact on the ICER was assessed in the range ± 0.25 dB/year. For first-line treatment effects, an improvement in effectiveness increased ICERs. The M70 cohort surpassed the £30,000 per QALY mark at –0.15 dB/year, while the F70 cohort exceeded this ceiling ratio at roughly –0.3 dB/year; the F50 and M50 cohorts did not surpass the £30,000 per QALY mark. When second-line treatment effects were examined, improving intervention effectiveness increased ICERs in the M50 and F50 cohorts and decreased ICERs in the M70 and F70 cohorts. However, the £30,000 per QALY mark was only surpassed by the M70 cohort when the treatment effect was equal to approximately –0.6 dB/year.

Figure 2-3: One-way analysis of treatment costs. (a) First-line treatment costs, baseline = £696.49; (b) second-line treatment costs, baseline = £784.28, (c) third-line treatment costs, baseline = £970.40.

a)



b)



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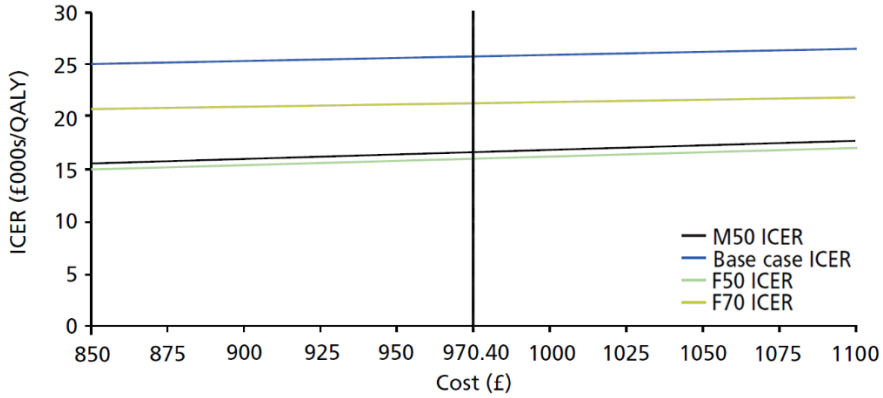
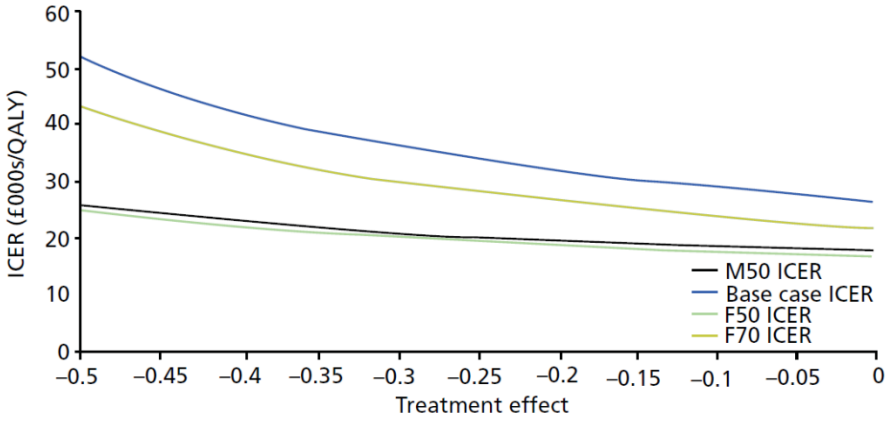


Figure 2-4: One-way analysis of treatment effects. (a) First-line treatment costs, baseline = 0; (b) second-line treatment costs, baseline = -0.74; and (c) third-line treatment costs, baseline = -1.22.

a)



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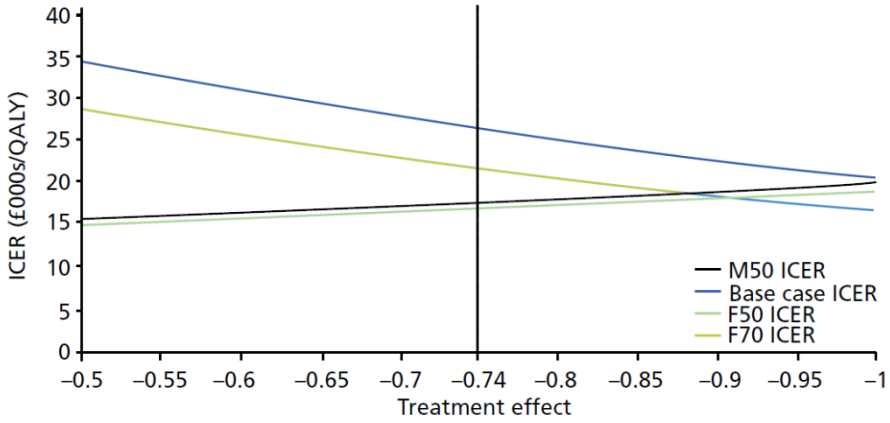
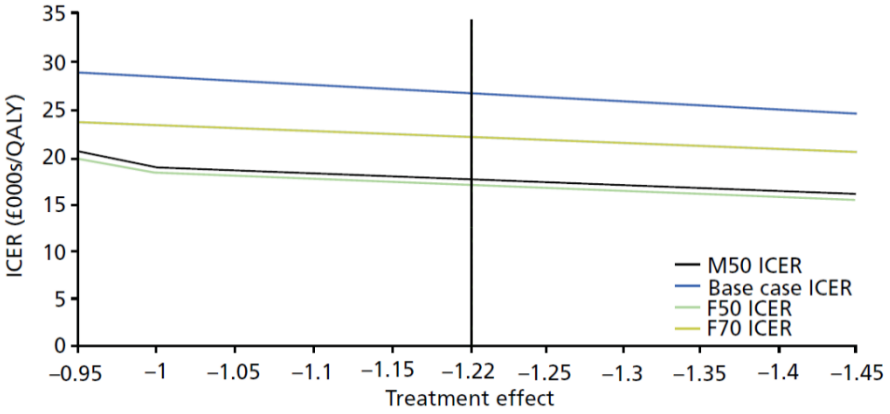


c)



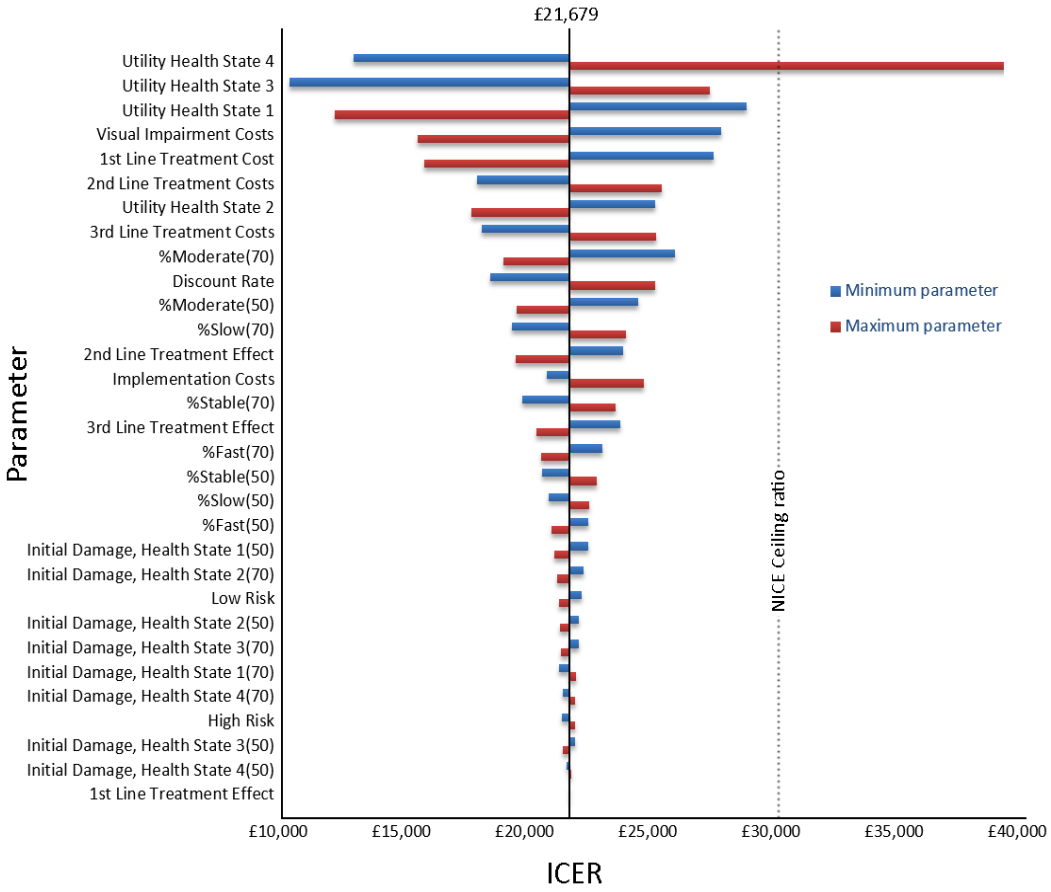
The costs of implementing proposed practice, the costs of patients progressing into a state of visual impairment and the time horizons utilised in the model were also chosen for one-way analysis for validation purposes. Implementation costs were varied between £0 and £900,000 in £100,000 steps and the impact on the ICER was assessed from a baseline of £410,000. Increasing implementation increased ICERs in all cohorts; the £30,000 ceiling ratio was exceeded in the M70 cohort only when this cost was equal to roughly £800,000. Costs of visual impairment were expanded to £9000 per subject in £1000 increments from the initial baseline assumption of £0 as a result of the NHS perspective of the model. As visual impairment costs increased, ICERs decreased for all cohorts, with the total cost associated with current practice superseding that of proposed practice over the 25-year time horizon at approximately £5000 for the M70 cohort, £4000 for the F70 cohort and £2500 for the M50 and F50 cohorts.

The impact of the time horizon was examined at 5-year intervals in both directions. For all 70-year-old cohorts, ICERs were observed to begin plateauing after 15-year time horizons; however, ICERs grew exponentially below 15 years. For the 50-year-old cohorts, ICERs were observed to continually shrink as time horizons expanded with reductions beginning to plateau after a horizon length of 45 years. All cohorts surpassed the £30,000 per QALY mark when the time horizon was shortened to approximately 10 years in length.

2.4.3 Deterministic sensitivity analysis: Tornado Diagrams

Tornado diagrams were constructed to represent model outcomes for the limits associated with each parameter, thereby mapping how the maximum and minimum values impact on ICERs. In addition, the costs associated with progressing into visual impairment were also explored using deterministic sensitivity analysis. For all parameters utilised within the model, outcomes were sorted in order of ICER impact, resulting in the tornado appearance. Tornado analysis was consequently performed on the full simulation results that the model derived (see Figure 2-5).

Figure 2-5: Tornado analysis of baseline parameters used in the model.



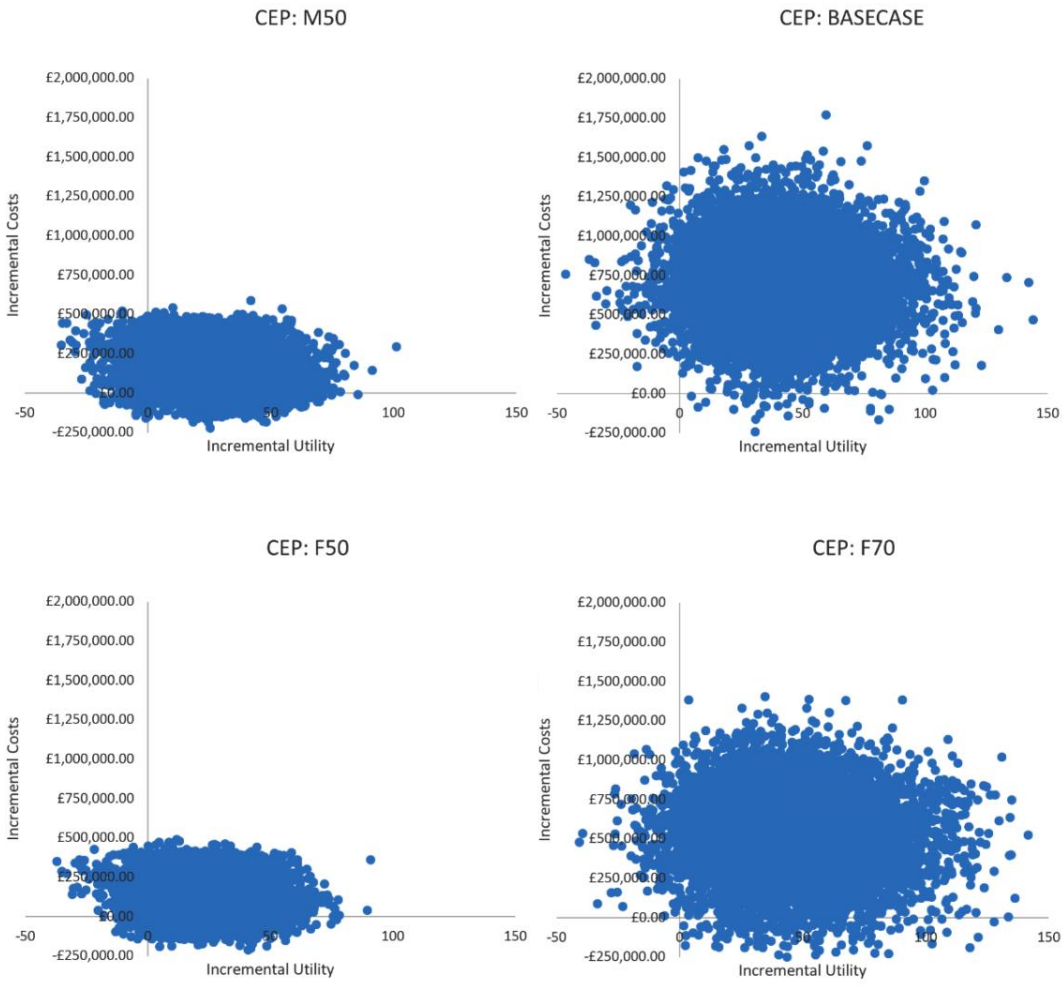
When analysing the full simulation data, utility health states were found to have the greatest impact on the derived ICER. In particular, utility health state 4 had the most significant impact, with findings suggesting that the variability around this parameter was sufficient to push the ICER beyond the £30,000 ceiling ratio. The projected cost of visual impairment was the next most important factor in the tornado analysis, altering the ICER by ±£12,326.98, with the lowest estimation of visual impairment costs sufficient to push the ICER beyond the £30,000 per QALY mark. Costs associated with the different treatment modalities were the next most important parameters with the variability around the cost of first-line treatment affecting the ICER most, followed by second- and, then, third-line treatments. The percentage of patients with a moderate rate of progression in the 70-year-old cohorts featured next in the diagram, followed by discount rate. All other parameters had less than a £5000 impact on the ICER from the minimum to maximum value.

When deterministic sensitivity analysis focused specifically on the M70 cohort, a greater number of parameters pushed the ICER beyond the £30,000 per QALY limit, including the

utility associated with health states 1, 3 and 4, the costs of visual impairment, the costs of first- and second-line treatments, the proportion of patients with moderate or slow progression in the 70-year-old cohorts and, finally, the effects associated with second-line treatment. Within the M50 and F50 cohorts, the only parameter observed to drive the ICERs beyond the £30,000 cut-off was the cost of visual impairment. For the F70 cohort, utility health state 4, costs of visual impairment and percentage of patients with moderate VF progression forced ICERs beyond NICEs ceiling ratio

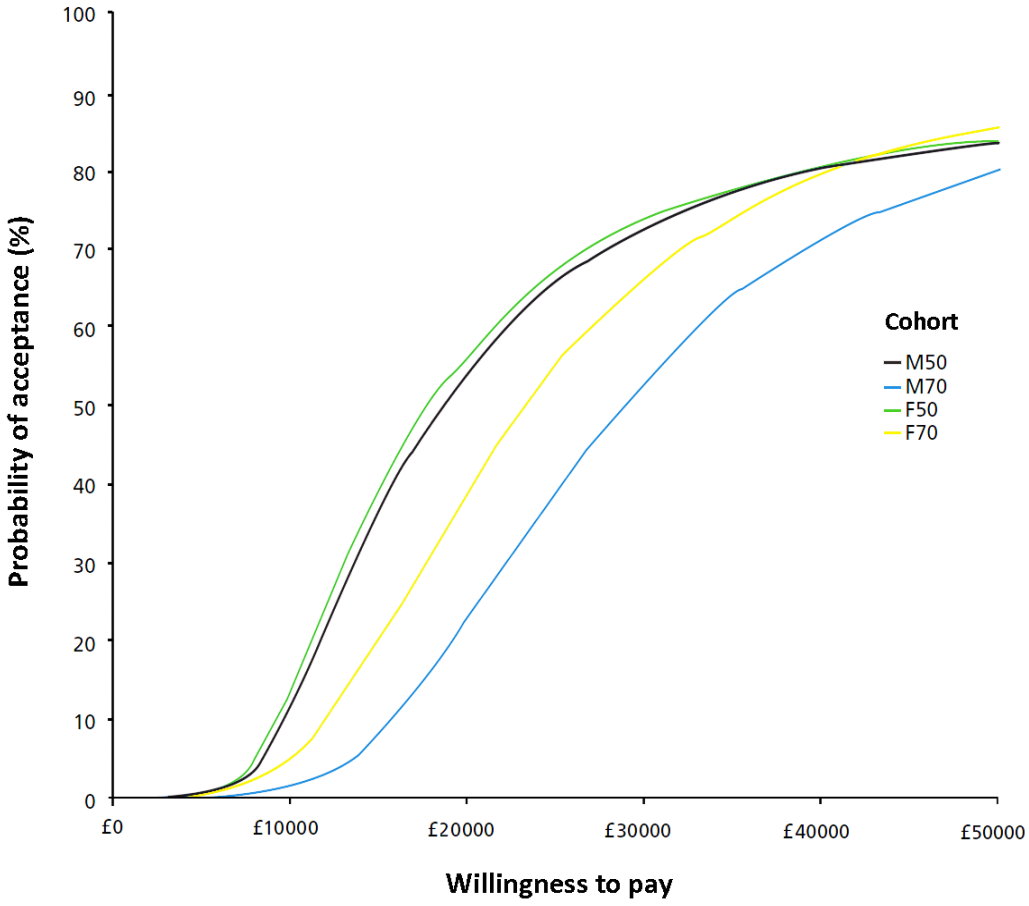
2.4.4 Probabilistic Sensitivity Analysis

Figure 2-6: Cost-effectiveness planes by cohorts studied



Greater variability was observed in CEP plots for the 70-year-old cohorts than for the 50-year-old cohorts (Figure 2-6); simulated incremental costs associated with the 70-year-old cohorts were considerably higher than those associated with the 50-year-old cohorts because more older patients were simulated in the model, while incremental utilities were also significantly higher in the 70-year-old cohorts than in the 50-year-old cohorts. In addition, there were twice as many observations in the north-west (dominated) quadrant of the plane in the 50-year-old cohorts (M50 = 540, F50 = 578) than in the 70-year-old cohorts (M70 = 211, F70 = 219).

Figure 2-7: Cost-effectiveness acceptability curves (CEACs) across all cohorts studied.



Subsequently, CEACs were defined from these simulations (Figure 2-7). Willingness to pay for each QALY gained was varied from £0 to £50,000 and the proportion of simulations deemed acceptable at this level was noted. Similarly shaped CEACs were observed for the M50 and F50 cohorts, and for the M70 and F70 cohorts. At a £30,000 cost per QALY

ceiling ratio, the proportion of observations deemed acceptable in the M70, F70, M50 and F50 cohorts was 57.33%, 67.78%, 73.36%, and 74.26% respectively. When the ceiling ratio was increased to £50,000 cost per QALY, the proportion of observations deemed acceptable was 81.69%, 86.35%, 84.22%, and 84.44% for the M70, F70, M50 and F50 cohorts respectively. The 50-year-old cohorts' CEACs were observed to plateau sooner than those for the 70-year-old cohorts, with the M70 cohort CEAC consistently lower than in other cohorts in terms of probability of acceptance. The F70 cohort's CEAC was consistently lower than those from the 50-year-old cohorts up until the £42,000 per QALY mark, at which point its ICER had an increased probability of acceptance compared with the 50-year-old cohorts.

2.4.5 Deterministic and probabilistic sensitivity analyses in combination

The DSA of VF costs, discount rates, risk distributions and costs of visual impairment was combined with PSA in order to examine how variation in this specific parameter may impact on the probability of acceptance for proposed practice at given willingness to pay. In terms of VF costs, analysis was varied from the baseline of £56.54 and varied from a maximum of £70.45 to a minimum of £38.76. In the base case analysis at a £30,000 willingness-to-pay threshold, an increase in the cost of a VF test reduced the probability of proposed practice being cost-effective from 57.33% to 45.63%, while the low estimation increased probability to 71.11%. Altering this cost in the other cohorts produced similar results, but with a smaller percentage change, particularly in the 50-year-old cohorts.

In terms of discount rates utilised, analysis was started from the baseline of 3.5% and varied from a maximum of 5% to a minimum of 0%. In the base-case cohort with a £30,000 willingness-to-pay threshold, the removal of discounting increased the probability of cost-effectiveness from 57.33% to 71.91%, while an increase in discounting reduced this probability to 49.13%; similar results were identified in the other cohorts. The differences in the probability of cost-effectiveness between the low discount and high discount were found to reduce as willingness to pay per QALY gained was increased.

In terms of the risk distributions assumed within the model, analysis started at the baseline of 80% low risk and 20% high risk, and this was varied from a ratio of 70% low risk and 30% high risk to 90% low risk and 10% high risk. In the base case with a £30,000

willingness-to-pay threshold, a decrease in the proportion of high-risk patients increased the probability of cost-effectiveness from 57.33% to 57.34%, while an increase resulted in a reduction of probability to 55.06%. These findings were generally reflected in the other cohorts.

Finally, in terms of the costs of visual impairment, analysis was varied from a baseline of £0 and varied from a maximum of £1758.50, the maximum degree of visual impairment costs before current practice became dominated by proposed practice. The introduction of costs of visual impairment to the base case increased the probability of proposed practice being cost-effective with visual impairment costs of £250, £500, £750, £1000 being associated with an increase in probability of 4.04%, 5.87%, 9.68%, 12.76% and 86.73%, respectively, at the £30,000 willingness-to-pay threshold.

2.5 Discussion

2.5.1 Summary

The study described in this chapter sought to examine whether or not increased VF monitoring at the earliest stages of disease identification (i.e. six VF tests in the first two years after diagnosis) would be cost-effective compared with the current practice of one VF test per year. The economic evaluation results show that proposed practice is associated with higher costs, but more QALYs, than current practice. Under the full simulation, the ICER was £21,679 and 834.65 years of visual impairment were avoided with proposed practice (10,000 individuals). When the model was run for the male cohort who were 70 years old (lowest residual life expectancies relative to the other cohorts), the ICER rose to £26,531, with a probability of being cost-effective at 57.3% at £30,000 threshold value. Since the economic model was constructed from the perspective of the UK NHS, when societal gains are accounted for (the costs of visual impairment beyond the UK NHS), the cost-effectiveness of proposed practice expands. Comprehensive DSA and PSA were performed. DSA identified that the ICERs were most sensitive to the uncertainty surrounding the parameters utilised for utility health states, particularly for utility health state 4, while the uncertainty associated with the costs of the different treatment lines was also found to impact on the derivation of the ICER.

2.5.2 Model baselines and patient characteristics

Key components of the economic evaluation of current practice compared with proposed practice were the patients' demographics and characteristics of their glaucomatous VF defects. This study incorporated a comprehensive analysis of VF data from four eye hospitals in England, comprising almost half a million VF tests. Just over 2% of the 50-year-old cohorts progressed at a 'fast' rate, while 4.22% of the 70-year-old cohorts progressed at this rate. While these percentages were notably small, the relative values were also of interest, as they provide evidence that older patients tend to suffer a faster rate of progression than younger patients, supporting recent published research (75). An attempt was made to ensure that the distribution of patients across different health states in the model was reflective of that observed in real clinics. For example, if the proportion of those already diagnosed with severe glaucoma or visual impairment in the model was overestimated, possible utility gains associated with proposed practice would be understated. Examination of the four VF databases revealed that more patients in the 50-year-old cohorts than in 70-year-old cohorts would be defined as having severe glaucoma, while the proportion of patients classified as visually impaired was similar in both cohorts.

2.5.3 Costs of treatment

Under one-way analysis, an inverse relationship was observed between first-line costs and cost-effectiveness of proposed practice while the converse was true for second- and third-line treatments. This can be explained by the fact that proposed practice is less biased towards first-line treatment than current practice; decision nodes indicated that first-line treatment is prescribed in 7 out of the 16 (44%) possible patient characteristic combinations when patients' rate of progression is unknown, while only 14 out of the 64 (22%) possible patient combinations were prescribed this level of treatment once rates of progression were identified. Proposed practice accelerates the time taken to identify the rate of progression and, therefore, first-line treatment is used to a lesser extent than in current practice. This implies that a reduction in costs of first-line treatment would reduce the cost of current practice more than proposed practice. Conversely, second- and third-line treatments are more prominent in proposed practice for the 70-year-old cohorts, causing ICERs to rise when the costs of these modalities rise. However, no major

impact was observed with an ICER of £26,907 and £26,629 when second- and third-line treatment costs were expanded to £900 and £1100, respectively, in the M70 cohort. Tornado analysis suggested that first-line treatment cost is the most sensitive parameter, followed by second- and third-line treatment costs; however, 50% variations in these parameters were not significant enough to push ICERs beyond £30,000 per QALY.

2.5.4 Health state utilities

Tornado analysis under full simulation identified utility health state 4 as the most important parameter impacting on the ICER and, at its highest estimation, the ICER expanded to £38,829. Furthermore, it was the only utility parameter to push the estimation of cost-effectiveness beyond the accepted NICE £30,000 per QALY ceiling ratio. It should be noted that the minimum value assumed for this parameter was adjusted to be equal to utility health state 3, implying that VF progression from severe glaucoma to visual impairment does not impact on patients' quality of life. Thus, investing in the implementation of proposed practice depends on reducing the number of patients making the transition to severe glaucoma, which is accordingly less cost-effective. Cohort analysis of health state utilities indicated that the sensitivity of this parameter varied by age group. While utility weight for visual impairment state was identified as the most significant parameter for the 70-year-old cohorts, utility weight for severe glaucoma was found to be the most significant in the 50-year-old cohorts. This was expected because, on average, disease stage is more advanced and progression faster in 70-year-old cohorts than in 50-year-old cohorts.

2.5.5 Treatment modality effects

Deterministic sensitivity analysis was also performed on treatment effects associated with each line of treatment to assess their impact on findings. Treatment effects play a prominent role in the derivation of cost-effectiveness, as the benefit of early identification of fast progressors is to provide them with a level of treatment that allocates resources efficiently; thus, if treatments were found to be similar in terms of effects, the benefits of proposed practice would not be realised.

One-way analysis of first-line treatment effects was found to produce consistent outcomes, with an increase in efficacy expanding ICERs at an exponential rate. These findings were consistent with expectations because increase in efficacy at the first line of treatment reduces the productive efficiency gains associated with moving patients to the second and third lines of treatment. The variation in second-line treatment effect impacted on the 70-year-old cohorts in a consistent fashion, with an increase in treatment effect reducing ICERs, while a reduction in treatment effect expanded them. For the 50-year-old cohorts the reverse was the case, with an increase in treatment effect expanding ICERs and a decrease contracting them. This can be explained by the decision nodes attributed to each cohort, as, when the 50-year-old cohorts were prescribed the same lines of treatment as the 70-year-old cohorts, the ICERs produced a similar pattern of results in both groups of cohorts. Third-line treatment outcomes were consistent with expectations, with expansions in treatment effects reducing ICERs as patients are moved to the third line sooner with the proposed practice compared with current practice.

Tornado analysis of treatment effects found none of these parameters pushed ICERs beyond £30,000 per QALY. Thus, the model implies that the costs of increasing VF monitoring after VF diagnosis, even in all patients, would not be prohibitive. In addition, first-line treatment effect did not impact on the full simulation or individual cohort ICERs as the model was specified such that patients receive this line of treatment before commencement of these strategies. Under the cohort analysis, treatment effects did not have a significant impact on ICERs, with second-line treatment effects observed to have the biggest impact, especially in 70-year-old patients as a result of the fact that older patients are more likely to be conferred second-line treatment than third-line treatment compared with 50-year-old patients.

2.5.6 Modelled time horizons

One-way analysis of the time horizon utilised was performed in order to assess how cost and utility streams impact on the derived ICER. Within the context of this study, proposed practice frontloads costs as extra VF monitoring takes place at the early stages of analysis. Consequently, as the time horizon was contracted, the ICER for all cohorts became less cost-effective, especially as time horizons approached 5-year levels. Conversely, as time horizons expanded past 25 years, marginal gains were achieved, but these were limited

by the residual life expectancies of the cohorts as a significant proportion of patients were absorbed by the death state after this period.

2.5.7 Sensitivity analysis

Cost-effectiveness acceptability curves were generated by varying willingness to pay; this analysis verified the hypothesis that the M70 cohort would provide the least cost-effective results with probabilities of acceptance lower than all other cohorts at all levels. The M50 and F50 cohorts produced similar outputs because of their similar residual life expectancies, and were more likely to be cost-effective as a cohort.

It was also observed that the probability of the F70 group being cost-effective increased at a greater rate than other cohorts as willingness to pay expanded. This is explained by the fact that an increase in willingness to pay acts as a greater constraint to the probability of acceptance for older patients than younger patients given their lower residual life expectancies.

Deterministic sensitivity analysis was then combined with PSA in order to examine interactions with the derivation of CEACs. Each parameter was marginally altered and CEACs were re-simulated to identify how these alterations impact on the probability of the proposed practice being acceptable at a given willingness to pay. Consequently, the impact of VF test costs, discount rates, risk distributions and costs of visual impairment on the CEACs was examined. The resultant CEACs produced rational results given the marginal variations in these parameters; however, it was noted that, in the case of the risk distributions, there was relatively little movement in the CEACs when this parameter was pushed to its rational limits. Furthermore, when costs of visual impairment were pushed to the limit identified as the watershed between which total costs of proposed practice became lower than those of current practice, the probability of acceptance of the proposed practice rose significantly, with low levels of willingness to pay still producing a considerable probability of acceptance.

The impact of VF test cost was larger in scale within the 70-year-old cohorts than within the 50-year-old cohorts, which was expected given that the younger cohorts have a longer period of time to recoup utility associated with the initial investment given their longer residual life expectancies.

2.5.8 Choice of model structure

The analysis performed in this study differs to that of van Gestel et al.(172) in several ways. A different type of model (Markov opposed to discrete event simulation [DES]) was used and a very different structural framework underpinning the models. Analysis of the cost-effectiveness of increased monitoring at the earliest stages of glaucoma identification was also undertaken. Van Gestel et al. chose to increase follow-up across the full horizon of analysis, which largely explains the differentials in ICERs associated with each study. In contrast to the findings of this study, the van Gestel et al. study suggests that reduced monitoring across their model's full treatment horizon may result in productive gains at specific willingness-to-accept thresholds.

Nevertheless, this study and the van Gestel et al. model is not directly comparable, with the latter focusing on lifelong IOP monitoring and management, whereas this study centres on VF progression. Furthermore, following NICE recommendations(38), this model primarily sourced data from the UK while van Gestel et al. used Dutch population data. Finally, this model had a single objective – to investigate the cost-effectiveness of increased early stage monitoring in the simplest, most accessible, method possible – whereas the DES model by van Gestel et al. aimed to provide a more complex and malleable model, therefore hindering comparison. However, it is worth noting that the economic model constructed in this study can be considered as a hybrid between Markov modelling and DES methods, as one significant benefit of the DES model is its ability to simulate patient characteristics within its framework, something that Markov models have not generally been able to do with transparency(173). The Markov model constructed within this chapter has been constructed such that its patient characteristics do inform how patients move across the model over time; patients' ages, genders and risk profiles are all taken into account within the model's decision nodes and, therefore, transition probabilities.

2.5.9 Clinical management

Intrinsic to any model mapping clinical management is ability to sufficiently replicate true practice. Economic models, whether in the form of Markov models or DESs, are relatively limited in their ability to reproduce clinical decision-making in the real world. This model sought to limit this constraint by seeking the advice of practising ophthalmologists in

order to provide interpretation of what informs clinical decision-making in glaucoma management. Clearly, decision-making can vary from clinician to clinician; for example, some clinicians may take a more aggressive stance than others when it comes to glaucoma treatment. Furthermore, while the clinical review panel was consulted during the formulation of the nodes, other glaucoma subspecialists may disagree with the step increases in treatment lines used. In particular, some clinicians may not subscribe to the view that the information gained from increased VF monitoring forms such a vital component in decision-making. Nevertheless, VF testing remains the only direct method for measuring patients' visual function and, therefore, to gauge if a treatment is effective in avoiding future impairment. Furthermore, in order to facilitate the transparency of the model, the decision nodes defining treatment pathways were simplified. As a consequence, it was not possible to include patient preferences in treatment prescription. Patient preferences represent a growing concern in health-care provision within the UK, with NICE explicitly identifying its incorporation as a key objective within its guidelines for treatment of glaucoma(127).

A key objective of NICE is to inform patients about treatments so that their preferences can be considered, maximising patient input. Within the context of the economic model here, it is possible that some glaucoma patients would wish to avoid surgical procedures despite being identified as fast progressors; this is important to bear in mind when interpreting the results from this model. If such a situation was included in the model, the cost-effectiveness of proposed practice would be reduced as the increase in power of information would not yield the same improvements in VF progression in these individuals.

In addition, it was assumed that patients entering into the model were immediately provided with first-line treatment, as this is usually prescribed as soon as an individual is identified as having COAG. This might be considered a limitation of the model. However, all patients were prescribed this treatment within the model's decision nodes so as not to derive an increase in treatment effect and therefore a reduction in probability of transitioning to a worse health state. A small subset of patients may not be not prescribed prior treatment, but the likelihood of this event was reduced by only including patients with significant VF damage at presentation (patients with an MD or pattern standard deviation outside 95% normal limits).

2.5.10 Trend of visual field deterioration

An assumption of the model is that progression of MD is linear. While many previous studies have modelled MD in this way(63) the analyses of VF data in this report provides evidence that this model may be an oversimplification. After bimodal stratification of patients' age, it was observed that a larger proportion of older subjects than of younger subjects progressed at a fast rate; this finding is also supported by recent research (174). Further studies are required to better understand the progression of glaucomatous VF loss and MD over time.

Within the Markov model, it was stipulated that stable patients would be provided with the same level of treatment as those identified as slow progressors. This stipulation is questionable as some clinicians may decide to monitor these patients less frequently if it appears that a reduction in quality of life will not occur within their lifetime. However, this would result in an increase in cost-effectiveness of early stage monitoring as, by removing or reducing treatment for this cohort, cost savings would be made without reducing the utility derived from proposed practice since disease is not worsening in this cohort.

This model, and others, also fail to take account of false-positive decisions that might arise from increased testing. No attempt has been made to consider the prospect of false 'overtreatment'. A discussion of this is given elsewhere(175). A development of the model should include some attempt to consider this important aspect of managing patient.

2.5.11 Costs within the model

Given results from a multisite clinical audit(1), it was assumed that existing service provision was performing at 100% capacity and that further infrastructure would be required in order to undertake proposed practice. However, efficiency gains in the management and organisation of VF testing may be possible. It was beyond the scope of this study to examine in detail the costs associated with extra resource use, but cost of implementation was incorporated into DSA and PSA to gauge its impact on final outcomes. A parameter value of £410,000 was varied between a derived minimum limit of £287,000 and a maximum limit of £820,000, resulting in ICERs of £20,770 and £24,706

(full simulation) and £25,398 and £30,303 (M70 cohort) respectively. These findings are very important because they indicate that uncertainty around implementation costs should not necessarily limit the final assessment of model outcomes, as the parameter was only found to surpass £30,000 per QALY by £303 in the cohort deemed to be the least cost-effective. However, it should be noted that alternative methods of calculating implementation costs exist. For example, if the additional VF tests required for proposed practice (40,000) were to be multiplied by the costs of performing VF tests (£56.54), an implementation cost of £2,261,600 would be arrived at. If this implementation cost was utilised within the model, a full simulation ICER of £35,352 would be identified, a figure higher somewhat higher than the £30,000 per QALY ceiling ratio associated with NICE. A scoping exercise about service provision for increasing VF testing is therefore recommended.

Under the current health economic model, a static interpretation of costs across the 25-year time horizon was adopted, which does not account for the impact of pharmaceutical patent expiry and, thereby, the introduction of generic pharmacotherapy. The accessibility of generic medications to health-care providers would reduce costs associated with all three treatment modalities, since each includes topical medication components. Given that both current practice and proposed practice incur medication costs, the impact of a reduction in such costs on the ICER is difficult to theorise, as these cost parameters interact with each strategy to differing extents. It is worth noting that medical costs may also expand as a result of the introduction of generic medications. LeLorier et al.(176) examined the impact of the launch of the generic substitution of lamotrigine (Lamictal®, GlaxoSmithKline, Brentford, UK), an anti-epileptic drug, in Canada between 2002 and 2006; the authors found that generic lamotrigine was associated with higher overall medical costs than the branded alternative because of increases in non-pharmacotherapy cost components of treatments.

The economic model was specified from the perspective of the UK NHS; consequently, it accounts for only direct costs of the disease and not for any indirect costs or social costs. This is an important limitation and has consequences on the precision of estimates for cost-effectiveness. Still, indirect costs and societal costs can only really add to the utility of the preferred practice. Previous studies have sought to quantify these costs in order to analyse their importance in glaucoma management and visual impairment. Lafuma et al.(136) estimated the non-medical costs associated with visual impairment in France,

Italy, Germany and the UK. Local prevalence rates of visual impairment were established along with estimates for the rates of non-registered visually impaired persons. Estimates of non-medical costs included institutional care, non-medical devices, residential adaptations, burden on carer, paid home help, loss of income and social allowances related to visual impairment. The main community cost components of visual impairment in the UK were loss of income (between 23% and 43%), burden on carer (between 24% and 39%) and paid assistance (between 13% and 29%). The authors also estimated that the total annual cost of visual impairment in the UK was €15.18bn. If indirect and social costs were included in the model, proposed practice would be more cost-effective. Proposed practice dominated (i.e. generated more QALYs at a lower average cost) current practice for a cost of visual impairment above £1758.50. Existing studies have found that the costs to society are possibly three times that amount(135, 177) suggesting there to be a stronger case for cost-effectiveness of increased early-stage monitoring when impact to society is accounted for.

2.5.12 Treatment effect deterioration

In the model, the impact of treatment effects on the rate of VF progression did not decline across the time horizon. However, the treatment effectiveness is known to fall between retreatment sessions, so the impact of treatment may be overstated in this model, resulting in a potential overestimation of cost-effectiveness. Nonetheless, this limitation was constrained by the inclusion of complex treatment regimens as identified with the study by Traverso et al.(134) who found that treatment defined by glaucomatous health state incorporated a range of treatment modalities spread over various time periods.

It was beyond the scope of the model to account for the development of side-effects that can occur as a result of glaucoma treatment. Modelling these factors is beyond the scope of this study, although the model did take into account treatment complications in terms of utility health states. Moreover, Burr et al.(161), in their derivation of the Glaucoma Utilities Index that was employed here, identified local side-effects as one of the least important factors informing quality of life, but this is still open to debate and further study.

2.5.13 Future research

Successful clinical management of glaucoma means making correct decisions about intensifying treatment, or initiating intervention, when patients are at risk of developing visual disability. Yet little is known about what VF defects at different stages of glaucoma specifically affect patients' abilities to perform everyday visual tasks. Various studies have looked into differing methodologies of identifying and quantifying the relationship between quality of life and deteriorating health states caused by glaucoma(101, 160, 178-180). In addition, little is known about ways in which patients can adapt to conditions in order to limit the impact on self-reported quality of life and the derived QALY estimates(181). In such situations, factors such as patient characteristics and the time from diagnosis can significantly impact on QALYs associated with differing health states of the disease, with their quantification possibly being overestimated. Economic models using these quality-of-life metrics may, therefore, overestimate the benefits of strategies such as the one proposed in this study; further research is required.

In addition, further analysis of the cost of implementing a strategy to increase early-stage monitoring of glaucoma is required. While this economic model found the strategy to be cost-effective, it was identified that an alternative methodology of calculating implementation costs would derive different results. To accurately define this cost, the existing spare capacity within the UK NHS glaucoma services needs to be quantified in order to inform how much extra infrastructure is required to increase monitoring, as the investment in this infrastructure could play a significant role in whether strategies, such as the proposed practice studied here, are cost-effective.

The wisdom of relying on a simple measure such as change in MD over time to identify a trend towards VF deterioration requires further examination to improve the accuracy of economic modelling in glaucoma. It may be advisable to also consider other characteristics beyond MD, such as the location of damage when considering VF progression. Finally, it seems practical to consider stratifying patients to less or more intense VF testing, with an idea of moving away from one diet of testing to fit all. For example, it would be useful to investigate whether the reliability of test results varies according to the approach taken. Although this study has illuminated the benefit of getting more perfect clinical information, it must recognise that perimetry still seems to be an imperfect test(182-184).

2.6 Conclusion

In conclusion, this study supports the recommendation by NICE for a randomised comparative trial (RCT) to assess the real-world implications of increased monitoring at the earliest stage of glaucoma identification. In particular, the health economic model described in this chapter has demonstrated that this proposed practice is likely to be cost-effective and the analyses revealed little evidence to suggest that the strategy would not be cost-effective. Further studies of the impact of the glaucoma on the quality of life of those with the condition are required to further the understanding of the cost-effectiveness of proposed practice, as sensitivity analysis suggested that health state utilities have a considerable influence on ICER results. In addition, the impact of diagnosis of glaucoma and subsequent 'adjustment' to the condition(184, 185) needs to be considered, as this may negatively bias patients' perceptions of quality of life with glaucoma and, therefore, quantification of utility.

Chapter 3: Disease severity in newly diagnosed glaucoma patients with visual field loss: trends from more than a decade of data

The work reported in this chapter formed a paper in *Ophthalmic and Physiological Optics(2)*; see List of Supporting Publications. The results of this chapter have also been presented as a read paper at the Association for Research in Vision and Ophthalmology (ARVO) meeting, Florida, USA, May 2014, the International Perimetry Society (IPS) meeting, New York, September 2014, and the UK and Eire Glaucoma Society (UKEGS) meeting, Bristol, November 2014. Trishal Boodhna performed the statistical analysis of the data and led the write up of the manuscript, Professor David P. Crabb conceived the study and oversaw the drafting of the manuscript.

3.1 Introduction

The health economic model described in the previous chapter is reliant on accurate quantification of the parameters. One aim of the work described in this chapter is to consider the accuracy of the distribution of existing health states in which glaucoma patients are entering into the model. This parameter is particularly important as it represents the "proportion of vision" that can be "saved". For example, if the vast majority of patients were identified as having already progressed to a state of visual impairment at detection, then there is little benefit that increased monitoring can yield. Whilst sensitivity analysis indicated variation in individual proportions of existing health states did not vary the ICER beyond NICEs £30,000 hypothetical ceiling ratio, it should be noted that these health state distributions are interdependent, so an increase in one health state distribution will necessarily lead to a reduction in another. Given its univariate nature, deterministic sensitivity analysis can only examine one parameter at a time and may therefore not accurately indicate the degree of impact on the ICER, making it important that proportions are ascertained as precisely as possible. The analysis

undertaken in this chapter therefore seeks to refine the method of data extraction from the Medisoft database in order to increase the confidence around the inputs utilised in the Markov model. The methods identified in this study were then re-employed (with reconfiguration to focus on the patients worst eye) in the Markov model that was constructed in Chapter 5 of this thesis, resulting in more robust model outcomes. This same process was also undertaken for the methods identified in Chapter 4 of this thesis, with the model in Chapter 5 again being updated to reflect the more robust data.

Beyond health economic modelling, late presentation with advanced disease in itself is a risk for an adverse long term outcome and worthy of study. There has been, for example, calls to increase the speed of service delivery to patients and to better identify those in most need(150, 151). A population screening programme for glaucoma would not be cost-effective and there is no existing national glaucoma detection strategy(63). In the UK, the vast majority of glaucoma cases are opportunistically identified by community optometrists during the course of a routine eye examination(63). Glaucoma suspects are then typically referred to secondary care for further examination and definitive diagnosis. An evidenced based debate about alternative referral pathways for glaucoma in the UK, in order to constrain the growing burden on hospital eye services, is ongoing(138, 139, 186-190). Adding to this debate is not the subject of the work described in this chapter, but developing methods for auditing and monitoring aspects of detection and diagnosis is useful as service delivery comes under scrutiny.

The utility of large-scale electronic records from routine clinical practice is beginning to be realised in clinical research, generating important and exciting findings(191). There are some good recent examples of this type of research methodology used in ophthalmology where examination of large data sets from several clinical centres can be used to complement information gleaned from traditional audits(192, 193). Automated perimetry has been widely used in glaucoma clinics for more than 20 years and large historical archives of digital VF records can be used to answer questions about health service delivery of glaucoma(153). Beyond the investigation of distributions of existing health states to improve the health economic model, a key aim of this study was to investigate trends associated with glaucoma detection in England. This study therefore also sought to examine whether patients are more likely to be diagnosed with less severe VF damage in recent years compared to the past. Specifically, the hypothesis that the

average severity of vision loss at glaucoma detection, in those diagnosed with a glaucomatous VF defect, improved over a 13-year period in England is tested.

3.2 Methods

Medisoft visual field databases (Medisoft Ltd., www.medisoft.co.uk) from different clinical centres in England were made available for this retrospective study. These archives contained 473,252 VFs from 88,954 patients from four centres: Moorfields Eye Hospital glaucoma clinic in London (320,334 VFs recorded between 1989 and 2012), Cheltenham General Hospital Gloucestershire Eye Unit (50,144 VFs; 2000–2011), Queen Alexandra Hospital in Portsmouth (31,879 VFs; 1999–2011) and the Calderdale and Huddersfield NHS Foundation Trust (70,955 VFs; 2000–2011). The study adhered to the Declaration of Helsinki and was approved by a research governance committee of City University, London. All the data were anonymised and transferred to a secure database. No other clinical data were made available apart from patient's age and the dates of the VF tests. Only VFs recorded on the HFA with the 24-2 test pattern, a Goldmann size III stimulus using the Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included for further analyses. This reduced the data to 423,194 VFs (83,573 patients) because a number of VFs recorded at one of the sites (Moorfields) in the earlier time periods were acquired using the older full-threshold algorithm.

The study population was defined as patients with measurable VF loss in at least one eye at diagnosis (at presentation to the clinic). Patients were only included if they had a VF with a MD flagged as outside the 95% normative limits by the HFA VF analysis software (MD < 2.07 dB)(113). This criterion had to be satisfied for at least two visits to the clinic to improve the precision of the estimate of an individual having glaucomatous VF loss, in the absence of any other clinical record. The MD in the worse eye (the one with the more negative value) at the first clinic visit was then taken as the surrogate measure of detectable VF severity at diagnosis. The date of the first visit and the age of the patient at that visit were recorded. The decision to examine the 13-year time period between 1st January 1999 and 31st December 2011 was made to maximise the equivalence of the contribution of data from the four centres. These inclusion criteria reduced the sample to 25,521 patient records. This reduced number of patient records, given the initial size

of the archive, simply reflects many of the recorded VFs are from sequences of follow-ups or are on suspicious referrals or glaucoma suspects.

Within the context of this thesis it is important to note that, whilst the health economic model focused on MD of the better eye, this study focussed upon the MD of the worse eye. As previously noted, worse eye MD is a good surrogate for 'level of disease' at case detection and trends in glaucoma detection are the focus of this study. Conversely, functional impairment for a patient is better related to the health of the better eye and functional vision and quality of life was the focus of the health economic model. The same methodology can be used to estimate better eye MD, and it is these results that are used to updated the HE model in the final chapter.

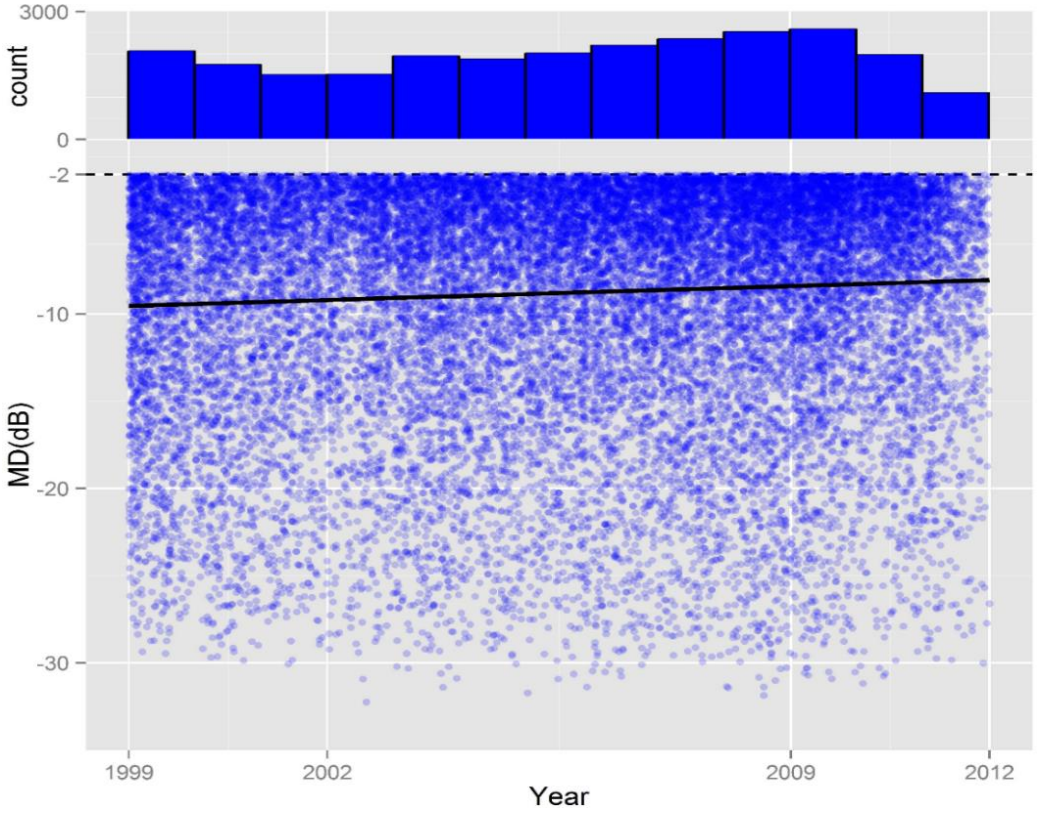
A linear model of VF severity, as estimated by MD in the worse eye, against date of diagnosis was constructed to examine trends over time, with a null hypothesis of average VF severity at the point of diagnosis not changing over the study period. Patients with MDs better than 6 dB in their worse eye were categorised as having early VF loss, whilst those with MDs worse than 12 dB in their worse eye were considered to have advanced VF loss. All other patients were considered to have moderate disease severity. These values were taken from a widely used criterion for glaucoma disease staging(162, 194). Temporal change in the proportion of patients in these categories was examined using a conditional density plot; this shows how a categorical variable, in this case severity of VF loss (early, moderate, advanced), changes over values of a continuous variables (time). All statistical analyses were carried out in the open source programming language, R.

3.3 Results

A scatterplot of VF severity, as measured by the MD in the worse eye, for each patient against date of diagnosis is shown in Figure 3-1 along with the trend line from the linear model. The slope of this line was positive, indicating average VF loss at diagnosis improved over the 13-year period by 0.11 dB per year (95% confidence interval 0.08–0.13 dB per year) and this was significantly different from zero ($p < 0.0001$). Median age of the sample of patients, at the date of diagnosis, was 67 (interquartile range 55–76) years. Linear regression revealed a statistically significant, albeit modest, relationship between

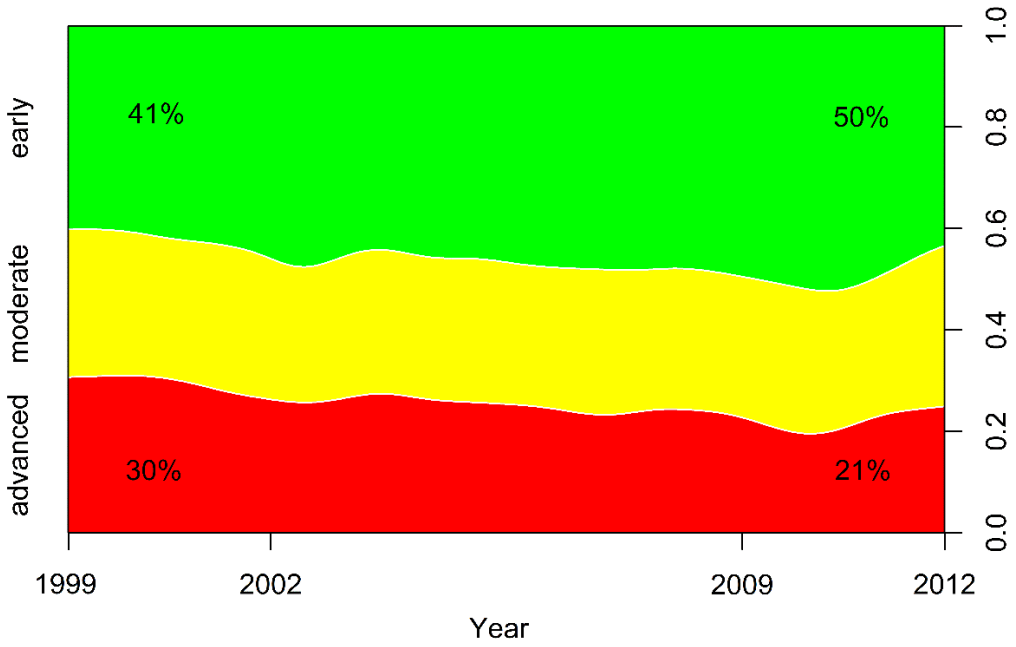
VF severity and age at diagnosis, with MD in the worse eye at diagnosis worsening by an average of 0.01 dB per year increase in age ($p < 0.0001$; $R2 < 1\%$). There was no relationship between age and time over the 13-year period, indicating that average age of the patient sample was not increasing with time ($p = 0.32$).

Figure 3-1: Scatterplot of MD in the worse eye for each patient against date of diagnosis (bottom). A histogram showing the number of patients by year (top); in most years there were approximately 2000 patient records.



The change in the proportion of patients categorised as having early, moderate or advanced VF loss in their worse eye at diagnosis over time is shown in Figure 3-2. The whole value percentage figures represent relevant proportions summed over the first (1999–2001) and last (2009–2011) 3 years of the study period: the average proportion of patients presenting with early VF loss increased from 41% to 50% ($p < 0.0001$; Chi-Square Test) whilst the average proportion of patients presenting with advanced VF loss decreased from 30% to 21% ($p < 0.0001$; Chi-Square Test).

Figure 3-2: Conditional Density Plot indicating the temporal change in the relative proportion of severity of VF loss (early, moderate, advanced) in the worse eye at diagnosis. The whole percentage figures are derived from the average of the first and last 3 years of data respectively.



3.4 Discussion

Average VF loss at the point of glaucoma diagnosis became less severe over the 13-year study period in England by approximately 1 dB per decade on the HFA MD scale. A recent modelling exercise, using data from some of the centres considered in this study, indicated that only a minority of patient eyes in secondary care (7–8%) progress at a rate worse than 1 dB per year(153). Therefore, one of these patients, diagnosed 10 years ago, would have, on average, progressed to a level of visual disability a year sooner than an equivalent patient diagnosed today because the VF loss would be more severe at the outset. This attempt to contextualise the improvement of detection of VF loss is hampered by several assumptions but illustrates the real clinical gains from these improvements in case finding glaucomatous VF loss are only modest. Similar conclusions were drawn from a long term trend study undertaken in Olmsted County with the authors observing that despite improvements in 20 year blindness probabilities being evident within their data set taking place over a 45 year time period between 1965 and 2009 a significant proportion of patients were still progressing to visual disability(195). On the other hand, by the end of the study period, one half of all patients newly diagnosed with

glaucomatous VF loss were detected with early VF damage in their worse eye; a significant improvement from a figure of 41% at the time of the beginning of the new millennium, a finding supported by O'Colmain and colleagues(196). This trend ought to reduce visual impairment because more patients benefit from earlier treatment to slow progression(78).

The results of this study only relate to the population of patients diagnosed with glaucoma with some VF loss in the first place and not those diagnosed on other clinical features of glaucoma, or those detected to be at risk because they have, for example, ocular hypertension. The measure of VF severity at diagnosis, HFA MD in the worse eye, is merely a surrogate and absence of a full clinical record means that it cannot be certified that all the patients have a diagnosis of glaucoma, or the date of a first VF record is the actual point of diagnosis. Nevertheless, the size of the data analysed, with more than 25 000 patients from four geographically different areas, ensures the estimates of level of VF loss at diagnosis in glaucoma are reasonable and informative.

Different factors might explain the observations drawn from these data. Detection may have improved because optometrists in the UK are increasingly well equipped(197, 198) and better trained(199) to detect glaucoma. Response to the NICE guidelines for the diagnosis and management of glaucoma published during the study period may also have contributed to the findings(127). Interpretation of the guidelines on case finding in glaucoma has, however, been controversial and these results do not specifically add to this debate; recent audits of full clinical records suggest more glaucoma referrals but the accuracy of these, as measured by the positive predictive value of diagnosis, has not improved(11, 200-202). One of these studies, considering data a year either side of the publication of the NICE guidelines, reported a significant improvement in the level of VF loss at presentation, and this supports the findings of this study(200).

Glaucoma is an age-related condition and there is an association between glaucoma severity and age(203, 204); an older patient, when compared to a younger one, is more likely to present with more advanced VF loss. This notion is only just supported by the very modest relationship seen between age and VF severity at diagnosis within this data. Since the population is getting older a negative temporal trend in later disease presentation might be expected and, therefore, these results showing a positive trend suggest the improvement in 'earlier detection of glaucomatous VF loss' is perhaps better than it seems. However, it is interesting to note that in this sample the average age of a

patient at diagnosis did not change over the study period. So testing the null hypothesis of no-change in VF severity at diagnosis was reasonable and supports the interpretation of the results that the improvement in 'earlier detection of glaucomatous VF loss' is modest at best.

These findings reiterate the well reported dilemma of many patients with glaucoma presenting themselves to eye specialists when the disease is already at an advanced stage: data at the end of the study period indicates that one-fifth of newly diagnosed patients with VF loss have damage that automated perimetry would classify as advanced in at least one eye. Research suggests these patients are, for example, likely to come from lower socio-economic groups, have no family history of glaucoma, do not have high intraocular pressure (IOP) and do not attend an optometrist regularly(150, 151, 204, 205). Population screening for glaucoma would reduce the incidence of late presentation of disease but has been shown to not be cost effective(63). Better case finding with development of community-based enhanced optometric services that may include a repeat measures scheme, coupled with sufficient financial incentive, is likely the best way to improve the accuracy of glaucoma detection and reduce late disease presentation(138, 139, 186, 190, 198).

Examination of the VF should be an important component of routine assessment for glaucoma and it is particularly important for detecting patients with normal IOP. Automated perimetry however is not considered an easy option for the suspect or the practitioner(206), and case finding results based on perimetry are subject to variability(207). Moreover, the mandatory contract for the General Ophthalmic Service for the testing of sight does not allow for repeat VF assessment. Obsession with 'preperimetric' glaucoma and newer technologies are not required to reliably detect early to moderate VF loss. Rather it is a case of incentivising the use of available technology, and using it appropriately in primary care that is more important – as articulated a decade ago(208) and, given these results, remaining true today.

Due to the retrospective nature of the study, there are certain limitations worth noting such as the absence of clinical knowledge about the individual patients examined. This is mitigated however by the fact that the study was based on a massive number of patient records drawn from repeat attendees of glaucoma clinics. Furthermore, whilst the study was multi-centred, the sampling of these was not done systematically. In addition, one of the centres, Moorfields, has an atypical profile of referred patients when compared to

other centres with a recent audit indicated that 39% of new referrals to the glaucoma service at Moorfields were initiated by optometrists and this rate is much higher elsewhere(201). Also, results are not applicable to other countries with different health care systems as data collected for this study was sourced from clinics based in England only. Moreover, the surrogate measure for glaucomatous VF loss (MD) could be affected by other visual comorbidities, especially vision loss from cataract. As there is no information on the history of patients studied, it is therefore not possible to ascertain whether improvements in MD over time have resulted from an increasing rate of cataract surgery in the population. No exclusion criteria based upon HFA reliability criteria were used because many were missing from the original databases. This is considered a limitation because VFs flagged as unreliable by these indices are typically excluded in clinical practice, although evidence of their usefulness is questionable(98, 99). It is assumed however that a similar proportion of VFs across all severities would have been excluded using these indices which would leave the main estimates unaffected. Capacity of the clinics sampled may also have changed over time but this would not affect estimates of the population of patients that have some form of VF loss at diagnosis. It may prevent consideration of all VFs being an estimation of glaucoma referrals, making it impossible to differentiate between suspects, patients or false positives. Finally, the data is not particularly 'current' because the database extractions were performed in 2012.

3.5 Conclusion

In conclusion this study provides some evidence that one aspect of glaucoma detection in England is modestly improving over time. It is more important to emphasise the data strongly suggests too many glaucoma patients continue to present to secondary care, and begin treatment, when disease is quite advanced in at least one eye. Whilst this study had no agreement to report differences in results between the four centres, this study still serves to highlight a novel idea of using large VF data archives to audit service delivery of glaucoma detection and monitoring across different centres and regions. Digital records from automated perimetry lend themselves to the task of electronic audits and this report ought to stimulate initiatives for glaucoma similar to those applied to other eye disease, like the UK National Ophthalmology Database programme(192, 209, 210). Aligning such data with health economic analyses, such as that undertaken in Chapter 2

of this thesis, can help identify methods to improve the efficiency with which glaucoma is managed in primary and secondary care, and help to reduce visual impairment. Following the methods identified in this study, the health economic model reported in Chapter 2 was updated to reflect the more accurate definition of the various health state distributions that patients could have in the better eye. The updated model is reported on in Chapter 5 of the thesis.

Chapter 4: Are rates of vision loss in patients in English glaucoma clinics slowing down over time? Trends from a decade of data

The work reported in this chapter has formed a paper in Eye(3); see List of Supporting Publications. The results in this chapter have also been presented in part as a paper presentation at the British Congress of Optometry and Visual Science (BCOVS), London, 2015. *Trishal Boodhna performed the statistical analysis of the data and led the write up of the manuscript, Luke J. Saunders assisted with the statistical analysis of the data, Professor David P. Crabb conceived the study and oversaw the drafting of the manuscript.*

4.1 Introduction

In continuation from Chapter 3, this chapter seeks to investigate further the parameters that form the foundation of the health economic model undertaken in Chapter 2. Whilst Chapter 3 identified methods to better examine the distributions of glaucoma severities at initial presentation, this chapter seeks to identify methods to better examine the distribution of rates of glaucomatous VF loss more accurately. As previously noted, rates of VF loss determined from a series of examinations in time can be clinically useful in managing a patient with glaucoma. They do however vary enormously among patients and can only be determined by observation of individuals. Recent studies, using data from treated patients in routine care, have yielded estimates for median rate of MD loss that vary considerably from −0.05 to −0.62 dB/year(211-214). Beyond helping to identify methods to improve the accuracy of the health economic model, adding to this literature by considering another large cohort of real-world data would be worthwhile. Furthermore, there does not appear to be existing studies considering how average rates of VF loss may have changed in the same sample of clinics over a significant period of time and this is the main idea explored in this paper.

Routinely collected clinical data can be used to assess real-world outcomes from implementing evidence-based findings from trials. These assessments can be carried out by taking advantage of large data sets collected from electronic patient records, and there are some good recent examples of this type of approach being used in ophthalmology(192, 193, 210, 215). Automated perimetry has been routinely used in glaucoma clinics for more than 20 years and VF data recorded electronically in many centres can be used to monitor trends in health service delivery of glaucoma(2, 153). This approach, using large-scale VF data, is adopted in the methodology of this study.

The first decade of the new millennium saw a shift to new topical treatment for glaucoma and ocular hypertension. For example, Owen and colleagues, using data from nearly a half of one million patients registered at 131 general practices across the UK, identified 2003 to be the year that number of prescriptions for prostaglandins overtook beta blocker-only medication. It remains unclear whether the introduction of these treatments impacted on disease progression in patients with glaucoma(152). This question is immune to a research study, no matter the experimental design. However, an objective of this study is to gather some insight by considering large-scale VF data recorded over a 13-year period in order to test the hypothesis that rates of VF loss differed in patients diagnosed before and after 2003. In addition, beyond developing methods to better identify the prevailing distributions of progression rates in the UK, this study also aims to describe the distribution of rates of VF loss stratified by age and severity of VF loss at baseline, along with a consideration of how these strata of patients may be followed more or less frequently during follow-up.

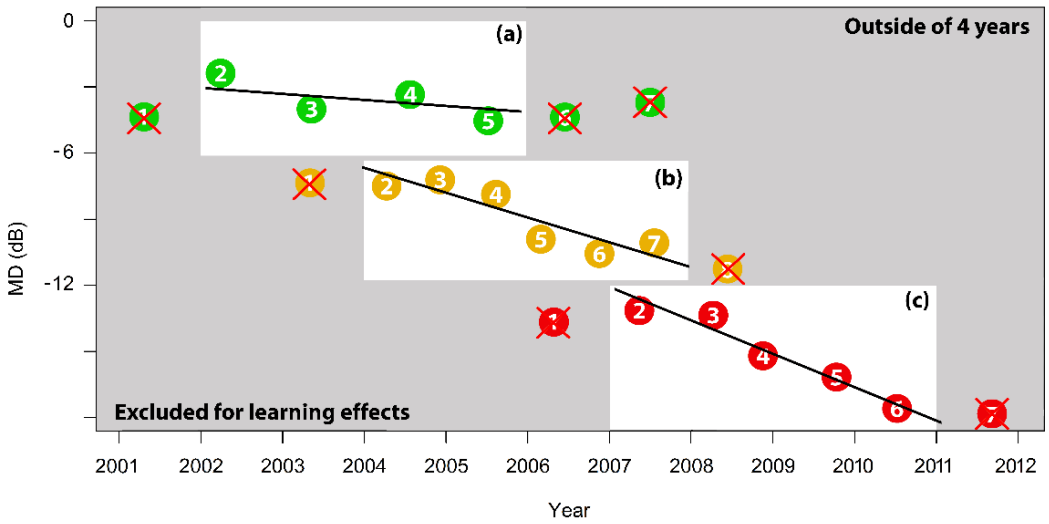
4.2 Methods

Medisoft VF databases (Medisoft Ltd., Leeds, UK) containing 473,252 VFs from 88,954 patients were downloaded in 2012 from glaucoma clinics at Moorfields Eye Hospital in London, Cheltenham General Hospital Gloucestershire Eye Unit, Queen Alexandra Hospital in Portsmouth and the Calderdale and Huddersfield NHS Foundation Trust. Data access was granted by the Caldicott guardians at each centre. All patient data were anonymised and transferred to a single secure database. No other clinical data were made available apart from patient's age and the dates of the VF examinations.

Subsequent analyses of the data were approved by a research ethics committee of City University London and this study adhered to the Declaration of Helsinki.

Only VFs recorded on the Humphrey Visual Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA, USA) using a Goldmann size III stimulus with a 24-2 test pattern acquired with the Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included, reducing the data set to 423,194 VFs. Series of data from patients >40 years recorded between 01 January 1999 and 31 December 2011 were then extracted with only those patients measured consistently with SITA Fast or SITA standard included.

Figure 4-1: A schematic illustrating the VF series inclusion criteria and method for calculating rates of MD loss (dB/year) for three example eyes detected in 2001 (a), 2003 (b), and 2006 (c). Eyes were excluded if <5 VF examinations or <4 years of follow-up. The first VF in each series was omitted to account for perimetric learning effects. Rate was calculated from linear regression of the baseline VF and the series of exams that fell within a 4-year period after it (white window). So, for example, for series (a) the sixth and seventh recorded VFs fall outside this window and are not used in the calculation. This ensures that all rates are estimated with equivalent precision allowing for comparisons over time. A minimum of three VFs were required to be in this 4-year window. This rate was then assigned to the date of the baseline exam.



Eyes with short follow-up (less than 4 years or less than five examinations) were excluded. The first VF examination in each series were then removed from further analysis to account for perimetric learning effects(91, 216, 217). Precision of estimating the rate of MD loss (dB/year) using simple linear regression varies enormously by the length of follow-up(218). An attempt was made to control for this by only calculating the rate within a fixed 4-year period (window) from the baseline test (see Figure 4-1). Each series

had to have at least three examinations within this period. Of course, this does not mean eyes with longer follow-ups were excluded. Yet, this fixed window was important for comparison of rates across the study period because those diagnosed at the start of the study period would have had much longer follow-ups than those towards the end of the study period.

A total of 18,926 eyes met the inclusion and exclusion criteria. These data represent patients in glaucoma clinics who are receiving routine care. Rates of MD loss (dB/year) were recorded and ranked by date of the baseline test. The data were then simply divided into two parts by chronological order. Thus, distribution of the rates of MD loss from baseline examinations in the first (15.01.99 to 16.09.03; n=9463 eyes) and second (17.09.03 to 05.09.08; n=9463 eyes) half of the study period could be compared. An eye, or a patient could only appear in one time period.

Furthermore, eyes with rates of MD loss better than 0 dB/year were defined as stable; those with rates between 0 and −0.5 dB/year were defined as slow rate progressors; those with rates between −0.5 and −1.5 dB/year were defined as medium rate progressors, whereas those with rates worse than −1.5 dB/year were defined as fast rate progressors. Temporal change in the proportion of patients in these categories was analysed with a conditional density plot; this shows how a categorical variable, in this case stable, slow, medium, and fast progressors, changes over values of a continuous variable (time or estimated date of diagnosis).

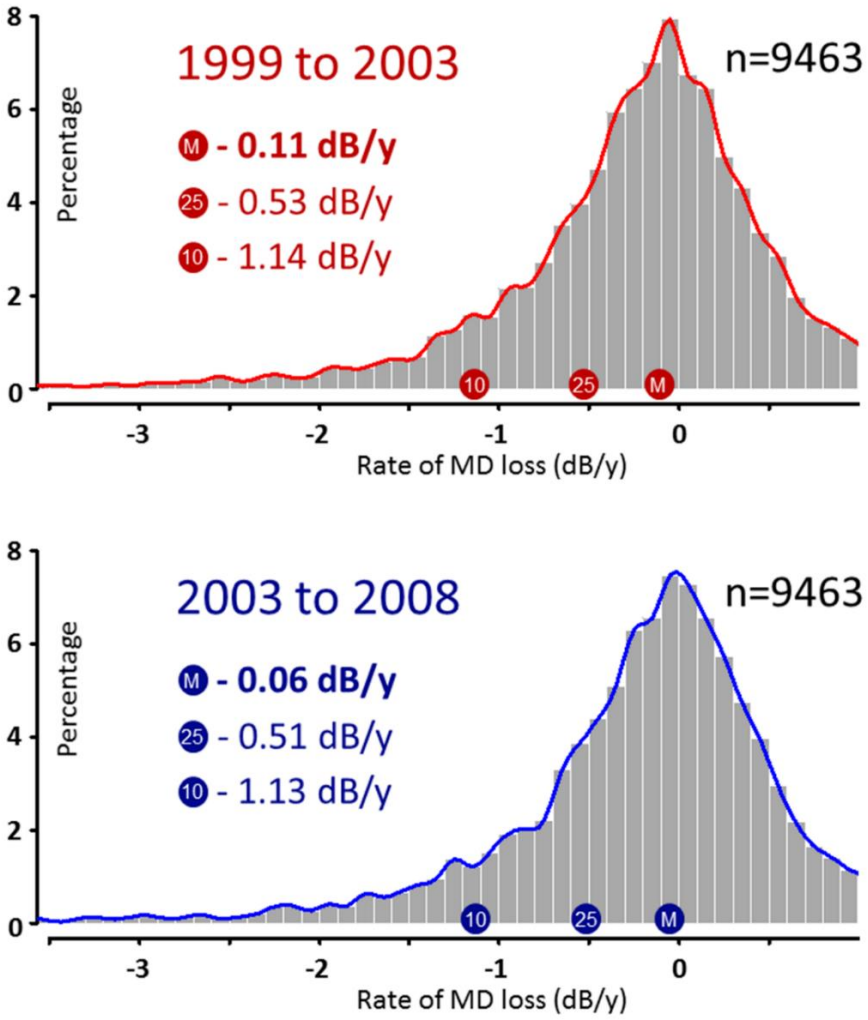
Eyes were stratified to determine the relationship between age and severity of MD loss at baseline with rates of VF loss. Eyes were stratified into simple age categories: younger patients (<60 years, n=6311) and older patients (>70 years, n=6385). All others were considered to be average age patients (n=6230). Eyes with MDs better than −6 dB, between −6 dB and −12 dB or worse than −12 dB were categorised as having early (n=10 920), moderate (n=3122), or advanced/severe (n=2063) VF loss, respectively. These values were taken from a widely used criterion for summarising disease stages in glaucoma and are represented within the colour schemes of Figure 1 (mild represented by green, moderate represented by orange, and severe represented by red)(162).

A simple metric for the frequency of examination during the 4-year follow-up period was also calculated. Eyes with three, four, or five examinations in this period were defined as receiving approximately ‘annual testing’. All others were considered to be having more

frequent VF surveillance. The percentage of eyes that had annual testing was then compared across the disease severity and age strata. This metric was also calculated for eyes with progression rates between 0 and 0.5 dB/year, 0.5 and 1.5 dB/year, and worse than 1.5 dB/year being categorised as slow (n=5849), medium (n=3774), and fast progressors (n=1123), respectively. All statistical analyses were carried out using the open-source programming language, R(219).

4.3 Results

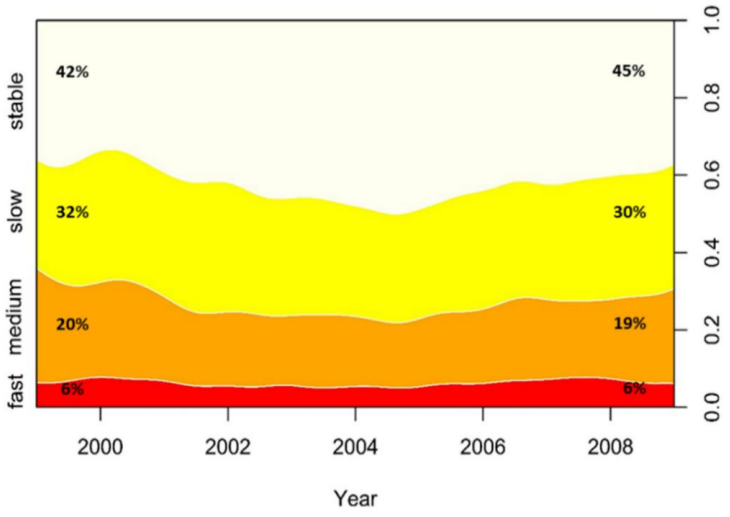
Figure 4-2: Distribution of MD rate in eyes diagnosed in two periods of the decade. Median, 25th (lower quartile), and 10th percentile are indicated. Curved lines represent a spline fit to the histogram. Note the histogram is censored at +1db/year.



In total, VF series from 18,926 eyes from 13,984 patients were analysed. Median (interquartile range) age, MD at baseline, and number of examinations in the 4-year follow-up were 65.5 (56.7–72.6) years, −2.8 (−6.6 to −0.7) dB, and five (four to five), respectively. The distribution of rates of MD loss (dB/year) in eyes diagnosed in the period 1999–2003 and 2003–2008 are shown in Figure 4-2. Although the median progression rate of theses distributions are different, indicating that average rates of VF loss slowed in the second period, the lower percentiles (25th and 10th) remained the same suggesting that there was no change in the proportion of patients who are more rapidly progressing. Median (interquartile range) age and MD at baseline in eyes diagnosed in the period 1999–2003 were 65.2 (56.4–72.2) years and −2.9 (−6.7 to −0.8) dB, respectively. Median (interquartile range) age and MD at baseline in eyes diagnosed in eyes diagnosed in the period 2003–2008 were 65.8 (57.1–73.0) years and −2.6 (−6.3 to −0.7) dB, respectively.

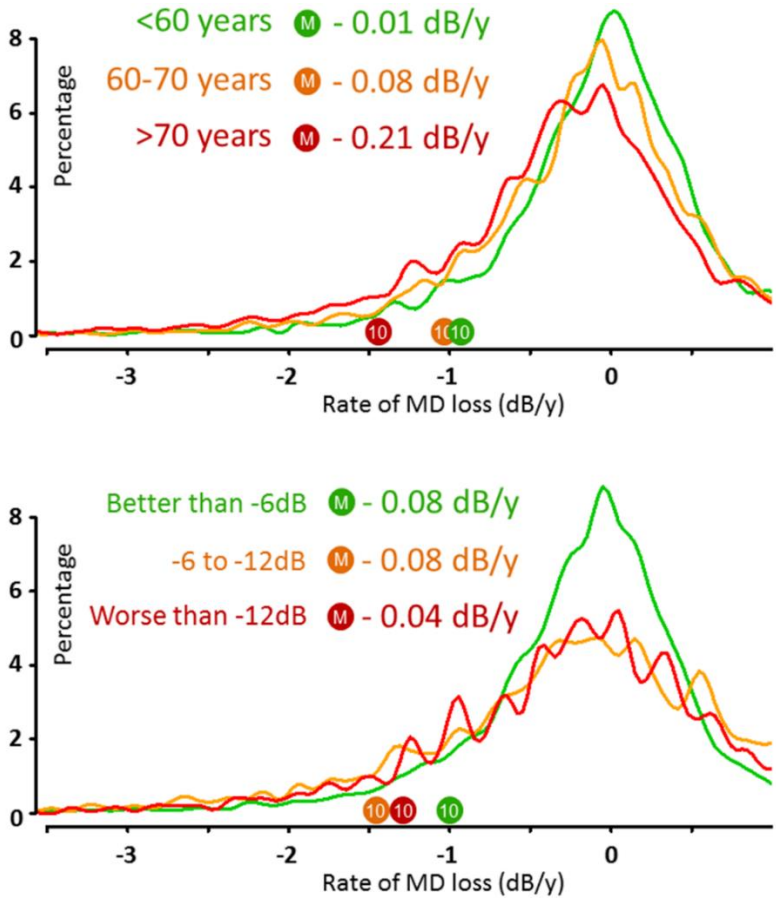
The change in the proportion of eyes categorised as having stable, slow, medium, or fast VF loss is illustrated in Figure 4-3. The percentage figures indicate the change in relative proportions of progressors across the two halves of the study period. It is noteworthy that the proportion of eyes defined to be medium or fast progressors remains largely the same over the entire study period.

Figure 4-3: Conditional Density Plot showing the temporal change in the relative proportion of eyes with different rates of VF loss (stable, slow, medium, fast), across the midpoint of the study period. A 3% increase in the proportion of stable progressors was identified in this study with a 2% and 1% reduction identified for the slow and medium progressors, respectively. No change was observed in the fast progressors.



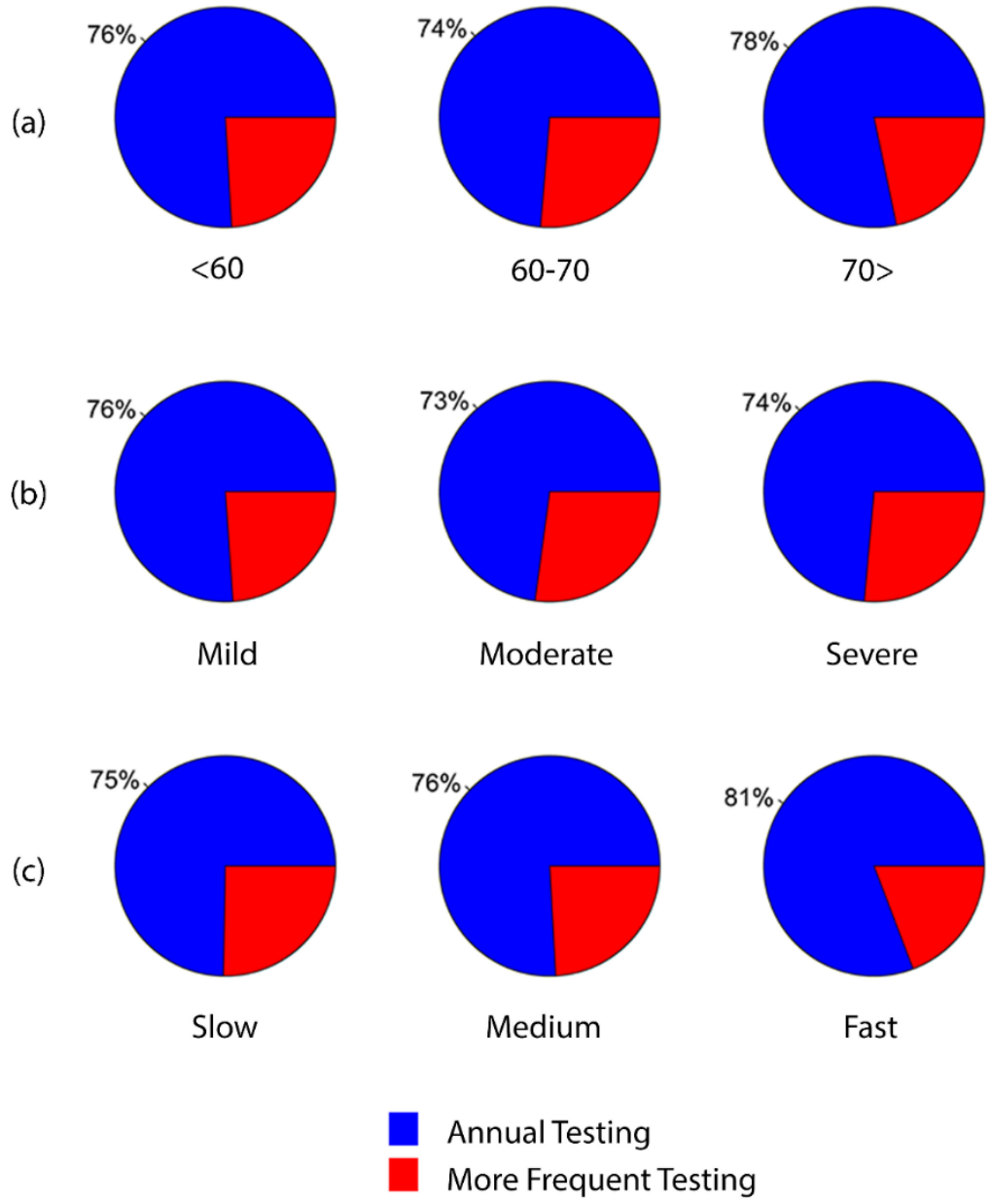
Distributions of progression rates by age and disease severity is illustrated in Figure 4-4. Older eyes (>70 years) were found to progress considerably faster than younger eyes (<60 years). Median rate of MD loss was similar across disease severity as measured by MD at baseline. However, inspection of the curves fitted to the histogram and the 10th percentile values suggest fewer patients with early VF loss (green) are likely to have rapid progression. At the 10th percentile eyes with mild, moderate, and severe damage progress at rates of −1.1, −1.5, and −1.3 dB/year, respectively.

Figure 4-4: Distribution (spline fit of histogram) of MD rate in eyes grouped by baseline age (top) and baseline severity of VF loss (bottom). Median and 10th percentile values are indicated over the study period.



The percentage of eyes receiving annual VF testing as stratified by age, severity of glaucoma, and rate of MD loss is shown in Figure 4-5. These data suggest that surveillance of patients with VF testing does not vary at all by age or stage of disease. More surprising, eyes losing vision quickly still mainly only receive annual VF testing.

Figure 4-5: Pie charts estimating the proportion of eyes receiving annual VF testing by (a) patient age (years), (b) glaucoma severity, and (c) glaucoma progression rate.



4.4 Discussion

Rate of VF loss (dB/year) is a straightforward concept. For example, an eye diagnosed with an MD of −8 dB will take 12 years to reach a level of assumed significant VF impairment (MD of −20 dB) if they progress at a rate of −1 dB/year. This is an oversimplification because impactful localised central and binocular VF loss is sometimes not best measured by a single perimetric index like MD. Still, these calculations are clinically useful when managing a patient over time, especially when decisions need to be made about intensifying treatment. Recently, Chauhan and colleagues (4) reported median (interquartile range) MD rate to be −0.05 (0.13, −0.30) dB/year in 2324 unselected manifest and suspect glaucoma cases. This study had an almost identical methodology and returned almost identical values albeit in a multicentre sample that was approximately six fold larger. Confirmation that patients under routine glaucoma care demonstrate slow rates of VF progression is important to report because other studies have not been equivocal about this(214).

The wide-ranging longitudinal data provides new knowledge about how MD rate might be changing over time. Interestingly, the median rate of MD loss was faster in patients diagnosed in the first half of the decade as compared with the second. This might be attributed to significant changes in the topical treatment of glaucoma patients and suspects which took place in the first part of that decade. The first randomised placebo-controlled trial to show effectiveness of prostaglandin treatment to preserve the VF has only recently been published, despite widespread use for many years(220). Owen and colleagues(221), using extensive GP prescription data, indicated prostaglandins became the dominant first-line glaucoma therapy in the UK in 2003, which conveniently coincides with the time point used to split the longitudinal data. On the other hand, in the absence of other information, the improvement in average MD rates might be attributed to changes in clinical management of cataract or other clinical management guideline changes during the 13-year period. Moreover, as is often the case, average values do not describe the entire distribution of the data. For example, the number of patients who were progressing rapidly did not change (Figure 4-3) and the 10th percentile of this distribution remained fixed throughout the period of follow-up (Figure 4-4). It would be fair to conclude that for the progression rates that matter most, there was no change over the time period observed. This historical trend reflects there not being a dramatic

change in treatment options for glaucoma, as there has been for other chronic eye diseases(222, 223).

Stratification of the sample by age revealed a clear relationship between the rate of MD loss worsening with older age. Patients over 70 years had considerably worse median rate of loss compared with younger patients. In this case, this large effect was applicable to the entire distribution of data (Figure 4-4) and this is noteworthy. This finding supports the results from other studies that have reported the same effect(224-226) and refutes the finding in at least one other study (albeit in patients with untreated normal tension glaucoma only) that there is no association between age and rate of VF progression(227).

The distribution of rate of MD loss also varied by baseline MD as indicated in the difference of the tails of the distribution rather than in the measures of central tendency in Figure 4-4. The 10th percentile for the distribution in the rates of loss from those patients with early VF loss indicated that rapid progressors are less likely to come from this group of patients when compared with those with moderate or advanced VF loss at diagnosis. This is revealing because it underlines the reduced risk of visual disability in those patients who are diagnosed in the earlier stages of the disease, not only because they have greater preserved vision to start with but they are, according to the data, less likely to progress rapidly than those patients who are diagnosed at a later stage(78, 228, 229). It is worth noting that the magnitude of this effect is, however, quite small. Moreover, precision of estimates of MD rates in individual eyes varies with VF damage and this has been established elsewhere(230). In other words, there is more variability in more damaged VFs, but this will likely not affect comparisons between such large groups of eyes.

A cross-sectional audit study conducted in several centres in England indicated that the large majority of patients have one VF examination per year(231) and this seems true for the patients observed over the period of time in this study. Recent research evidence, reflected in clinical guidelines, has suggested that more frequent VF testing would help to identify rapidly progressing patients and this would have both clinical and potential health economic benefits(1, 128). At the same time, this would require a shift in resources, clinician opinion, and patient views about automated perimetry(206, 232). This study clearly shows a worse rate of VF loss was associated with older age and, albeit to a lesser extent, level of VF damage at diagnosis. Yet most patients simply receive the same diet of testing over time (Figure 4-5). In other words, there was no evidence that

patients were stratified to receive more or less frequent examinations given their age, progression rate, or severity of glaucoma. In fact, it looks like there is a trend for patients with more rapid progression to less likely receive more frequent VF testing. There are certainly some interesting research studies that have recommended alternative types of VF follow-up schemes, in particular studies that have examined the clinical and cost-effectiveness of increased monitoring to detect fast progressors(1, 15, 175, 233), but these have yet to translate to clinical practice. It would be interesting to consider stratification of VF resources to patients who might benefit more or less from them and this ought to be a question for future prospective studies.

The main problem with the design of this study is the absence of any clinical indicators on the eyes other than the VF results. So, for example, there was no information about exact diagnosis, intraocular pressure, optic nerve head characteristics, individual patient history, or other risk factors. Likewise, there was no information about types of treatment and concomitant eye disease. At the same time, these data represent unselected people in glaucoma clinics who are receiving routine care. Moreover, the sheer size of the data provides interesting insights that might not be uncovered by controlled prospective studies on smaller numbers of people. This study has other notable limitations: it was multicentre but the sampling was not carried out systematically and the data are not particularly current because the extractions were carried out in 2012. Furthermore, HFA reliability indices are used to exclude poorly carried out examinations in clinical practice, but these were not used in this study because many were missing from the original database. A secondary argument that the strict inclusion criteria required for this study could have impacted results could also be made. In this study, VF data was excluded on the basis of undertaking multiple different testing algorithms, patients were therefore required to have undertaken only one form of testing algorithm in order to achieve data equivalence. It was rare however for patients to change testing algorithm across their historical VF testing history, exclusion by this criteria therefore would not impact results significantly. Data was also excluded on being outside the equivalence dates, therefore data from the 1980s were excluded as our time period focussed on VFs dated between 1999 and 2011. These VFs were few in number however so it was not expected to have introduced any exclusion bias to the study. It is also important to note that the exclusion methodology implemented within this study necessitates contraction of the data set. Eyes were required to have at least 5 VFs in order to ascertain an accurate estimate of VF progression and these had to be sourced over at least 4 years, and such criteria was

necessary to ensure robust and consistent estimations of rate could be achieved with equal degrees of precision.

4.5 Conclusion

In conclusion, the results from this study suggest that patients in clinics in England, on average, experience a relatively slow rate of VF deterioration. It is important to recognise, however, that a proportion of eyes progress at a rate sufficiently fast that is likely to result in a visual impairment classification within their lifetimes. Furthermore, although this study found that median rates of MD loss appear to be declining, it is of note that this trend was not evident in patients who matter the most; that is, individuals with medium to fast rates of VF loss. Of course, results refer to a patient population and have little bearing on the management of individuals. Yet, this study illustrates the use of large VF databases to monitor and audit service delivery of glaucoma treatment. Digital records from automated perimetry are amenable to electronic audits and this report seeks to motivate initiatives for glaucoma similar to those put into place for other eye diseases. These data can then be used in combination with health economic techniques, as performed in Chapter 2 of this thesis, in order to investigate potential efficiency gains within the treatment of glaucoma and potentially reduce the burden of visual impairment in the UK. As such, following the methods identified in this study, the health economic model constructed in Chapter 2 was updated to reflect the more accurate definition of progression rate distributions that were simulated, this time focusing upon the better eye only. The findings of this re-simulation are reported in Chapter 5 of this thesis.

Chapter 5: Update of the Health economic model and the evaluation of different monitoring intervals in glaucoma patients

The work reported in this chapter has formed a paper in BioMed Central: Health Services Research; see List of Supporting Publications. Trishal Boodhna undertook the health economic modelling, performed the statistical analysis of the data and led the write up of the manuscript and Professor David P. Crabb conceived the study and oversaw the drafting of the manuscript.

5.1 Introduction

This chapter seeks to investigate further the parameters that form the foundation of the health economic model undertaken in Chapter 2. Within Chapter 2, the cost-effectiveness of using different monitoring intervals to detect VF progression rates in all newly-diagnosed COAG patients using a health economic model developed for the purpose was examined. Two different VF monitoring schemes defined as *current practice* (annual VF testing) and *proposed practice* (three VF tests per year in the first two years after diagnosis) were examined within the model. Within Chapter 5, the constructed model is summarised and updated to examine the hypothesis that cost effectiveness improves by implementing *proposed practice* on groups of patients stratified by age and severity of glaucoma at diagnosis.

Furthermore, a new component of the model, estimating costs of visual impairment, is added. It is hypothesised that *proposed practice* applied to some groups of patients will yield improved clinical information and therefore increase the cost-effectiveness of clinical care. The outcome of this economic evaluation could potentially provide information to assist decision-makers in the allocation of the available resources so that

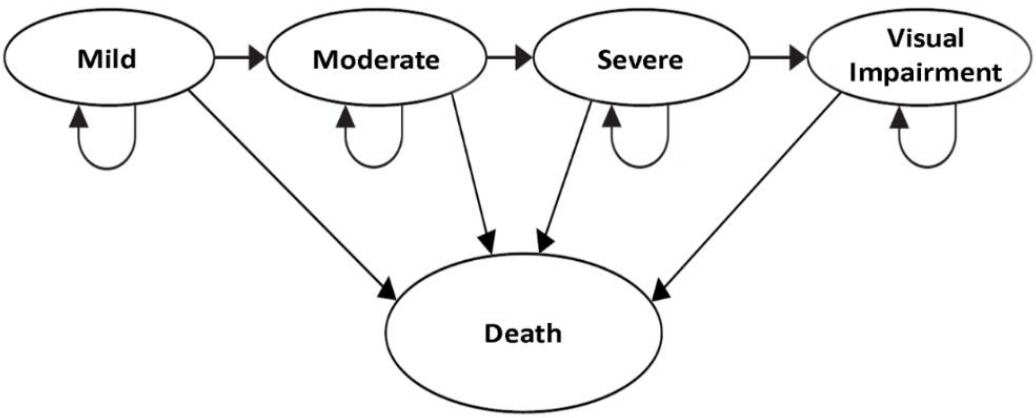
benefits can be maximised; it could also be used to help design an appropriate prospective study on frequency of monitoring in glaucoma.

5.1 Methods

5.1.1 Health economic model

The Markov model (see Figure 5-1) was constructed to compare *proposed practice* against *current practice* for patients with newly diagnosed COAG during a 25-year horizon. Markov models are commonly used for quantifying the costs and health consequences of patients moving through different disease stages over time(26, 234, 235). In the model, patients can start in any one of four states of severity of disease at diagnosis. It was assumed that one cycle through the Markov model is one-year long. In each cycle through the model, the costs and utilities are calculated for each cohort of patients. In a particular model cycle, patients can remain within their existing health state, or progress towards a worse health state. Progression towards a worse disease severity is the only possible transition because vision loss in COAG is irreversible. It is also assumed that patients move sequentially and cannot skip states due to the slow evolution of the disease. Patients may also leave the model and move into an absorbing state ('Death').

Figure 5-1: The structure of the Markov Model for glaucoma. Patients can only transition to the next state in sequential order, remain in the same state or be classified as deceased at each Markov cycle



The disease process in glaucoma is a complex multivariable one and long-term outcomes for individuals are often unpredictable. This model only conceptualises disease progression and its treatment as they manifest in clinical practice. First, the model is only applicable to patients that have a diagnosis of COAG as defined by NICE and is not relevant to patients with a diagnosis of ocular-hypertension or others that are at risk of glaucoma. Next, VF damage alone is used as a proxy for glaucoma disease severity. Disease progression is modelled by means of the speed (rate) at which the MD worsens. Then, a simplifying assumption was made that the effect of treatment lowers IOP, which in turn affects the VF progression rate and reduces the movement between the disease states. The model then assesses the impact of being able to institute treatment decisions earlier because of the better clinical information afforded by the *proposed practice* compared to *current practice*.

In order to reduce model complexity and allow simple decisions about treatment pathways it was assumed that a patient can be characterised according to four categorical variables at the point of diagnosis of COAG:

- *Age* (younger patient; older patient)
- *Severity of disease* (mild; moderate; severe; visually impaired)
- *Rate of progression* (stable; slow; medium; fast)
- *Risk of progression* (high risk; typical risk)

Age of patient is reduced to a dichotomous variable – the modelled younger and older patient has an age of 50 and 70 years at diagnosis respectively, making up 28.2 and 71.8% of the cohort respectively. The rationale for these values and distribution is detailed in the description of the model in Chapter 2. *Severity of Disease* (health states) was defined according to a commonly used classification of MD (194). Conveniently this scheme has been used in previous health economic models of glaucoma health service delivery and allows for use of utilities reported elsewhere(63, 236, 237). *Mild disease* is defined as VF loss with an MD better than -6dB. *Moderate disease* is defined as VF loss with an MD between -6dB and -12dB. *Severe disease* is defined as VF loss with an MD between -12dB and -20dB; very few of these patients would satisfy the visual field component for legal fitness to drive for example(113). Of course, people function visually with both eyes and

the better seeing eye is the best estimate of visual function(106). Therefore, these levels of disease severity were required to exist in the patient's better eye (defined as the eye with the better MD) since this best reflects the patients visual morbidity(104). Patients with MDs worse than -20dB were classified as *visually impaired* (132).

Table 5-1: Parameters for the updated model were estimated from a retrospective analysis of an electronic patient record containing 473,252 VFs downloaded in 2012 from Moorfields Eye Hospital in London; Cheltenham General Hospital Gloucestershire Eye Unit; Queen Alexandra Hospital in Portsmouth and the Calderdale and Huddersfield NHS Foundation Trust. Baseline progression rate and existing damage in the better eye were revised following the methods used in Chapter 3 and 4 examining levels of rates of loss and existing disease severity distributions at diagnosis)

Parameter	Stratification	50 y/o	70 y/o
Progression Rate Distribution	Stable (0 dB/year)	46.7%	37.9%
	Slow (-0.25 dB/year)	37.8%	36.6%
	Medium (-1 dB/year)	12.5%	19.1%
	Fast (-1.5 dB/year)	3.0%	6.4%
Health State Distributions	Mild (> -6dB)	83.0%	79.8%
	Moderate (-6dB to -12dB)	10.8%	15.0%
	Severe (-12dB to -20dB)	5.6%	4.1%
	Visually Impaired (<-20dB)	0.6%	1.1%
Initial Damage	Mild	-3.1 dB	-3.1 dB
	Moderate	-8.3 dB	-8.4 dB
	Severe	-15.5 dB	-15.4 dB
	Visually Impaired	-24.0 dB	-23.6 dB

Rate (Speed) of progression in an individual patient can be estimated from MD loss per year for patients using linear regression of MD against time(3). The more negative the rate the faster the progression speed. These rates are categorised as stable (≥0 dB/year), slow (between 0 to -0.5 dB/year), medium (between -0.5 and -1.5 dB/year) or fast (worse than -1.5 dB/year). It is important to note that observed rate of progression is only available to the clinician in the model when sufficient VFs have been done to precisely detect it - this is termed '*perfect information'*. It is therefore this variable that varies between proposed and current practice. *Risk of progression* in COAG is nebulous and

multifactorial. Apart from level of IOP, risk of progression is composed among other factors of baseline diagnosis of exfoliation syndrome, decreased corneal thickness, structural changes to the optic nerve head and the retinal nerve fibre layer and co-morbidity of other eye diseases(64). For this model, the simplifying step of denoting patients to have *high* progression risk or *typical* progression risk was taken and the input parameters were taken from the model described in Chapter 2. Consequently, at diagnosis of COAG, there are 64 types of 'patients' based on the permutations of the initial model parameters. The relative proportions belonging to each group were estimated from data observed in glaucoma clinics in England. For this chapter, figures for severity of disease and rate of progression were updated following the findings of Chapter 3 and Chapter 4 and these are summarised in Table 5-1. Whilst these chapters focussed upon the patient's better eye, Chapter 5 utilises the patient's worse eye as worst performing eyes are the driver behind decision making regarding treatment modalities. Therefore, whilst the methodology to derive data is the same, the final outputs differ due to the change in eye studied. Furthermore, the distribution of patients stratified by initial health state described in this Chapter varies from that observed in the distribution specified in Chapter 2 (Table 2.6). This is explained by the more refined inclusion criteria used with the Medisoft data set to identify initial health state distributions. Whilst the distribution for Chapter 2 was established by simply stratifying the dataset by age and disease severity, stricter inclusion criteria was used for this Chapter following the methods identified in Chapter 3 to better specify this distribution.

The health economic model simulates glaucoma progression in 10,000 hypothetical COAG patients stratified by age (50 and 70 years) and severity of glaucoma at diagnosis. The probability of transition to the next state in the model followed published methodology of Hernández et al.(236) and Briggs et al.(26); these are driven by the treatment pathways that are used to ameliorate the rate of progression. Again, these are detailed in greater depth in Chapter 2 but what follows is a short description of the principles underpinning them.

People newly diagnosed with COAG are offered 'pharmacological treatment' and this is denoted treatment pathway 1. Patients with COAG who are at risk of progressing to visual impairment despite this first line treatment are offered intensified treatment which might be surgery with pharmacological augmentation. Typically, this would only be done after an observing evidence of disease progression. It is this information that might be

yielded earlier by *proposed practice*. In the model in Chapter 2, this intensified treatment pathway is denoted as 2 or 3. The former would typically be combinations of alternative pharmacological treatments or 'laser treatment' whereas the latter would be trabeculectomy with pharmacological augmentation. To model the decision making process behind treatment allocation and its impact upon the probability of transition to worse states of disease, two ophthalmologists with a specialist interest in glaucoma, were consulted to construct simplified treatment pathways that patients would face in a NHS hospital setting.

For the model in Chapter 2, the treatment pathways are used in a time period denoted as *'imperfect information*', where the managing clinician is 'unaware' of the patient's true rate of VF progression, simply because they have not been monitored closely enough. After a defined number of VF tests, the patient's progression rate is identified, and then enter into a time period defined as '*perfect information'*. The clinician now has the opportunity to continue to provide the patient with the existing degree of treatment, or to intensify it. These pathways are linked by a series of decision nodes detailed in Chapter 2 (Table 2-3). As an example, a *younger patient* entering into glaucoma care at health state 1 (mild damage) and defined as being at low risk of progression would receive treatment pathway 1. If the patient was subsequently defined as having a fast rate of progression, then they would be moved to 3rd line treatment but only when the clinician has 'perfect information'. This functionality was built into the model in order to reflect the resource reallocation that occurs once the clinician identifies those patients who are potentially undertreated. This temporal improvement in patient management is what underpins this study, as the more expedient allocation of efficient treatment modalities differentiates the *proposed practice* from *current practice*. However, this reallocation comes at a cost and this is described briefly below.

A key component of the cost-effectiveness of *proposed practice* is the cost of additional resources for more VF testing. After all, this is seen as the main barrier for implementing increased surveillance and more examinations(232). Costs were sourced from the reference costs (170) and along with the costs of treatment, (derived from a study reported by Traverso et al.(134)) are taken directly from the model in Chapter 2. A further driver of the cost-effectiveness of the *proposed practice* is the quality-of-life improvement gained from reducing the chances of VF loss and visual impairment. In this study, utility weights associated with each health state were derived from those

developed and implemented by Burr and colleagues(63, 161). Consequently, those defined with mild, moderate, severe disease and visual impairment were attributed a utility of 0.8015, 0.7471, 0.7133 and 0.5350 per year respectively.

5.2 Model Analysis

The main outcome measure was the ICER derived by *proposed practice* as an alternative to *current practice* as applied to all newly diagnosed patients (full model). A further outcome measure was the years of healthy vision saved with *proposed practice* compared to *current practice*. Patients were then stratified into four groups with each of the four groups modelled separately to receive *proposed practice* while all other patients would receive *current practice*. The model results, with the ICER being the primary outcome, were then used to test the hypothesis that applying *proposed practice* to a specific group of patients would be more cost-effective than making it available to all newly diagnosed patients.

In the original model in Chapter 2, indirect costs of severe visual impairment from COAG were not included. These are governmental and societal costs for supporting a visually impaired person, such as visual rehabilitation, social services, or local authority care rather than costs of blindness to the individual. Estimating these costs is problematic, country dependent and tricky to establish(238). Still, some useful estimates are available (135); these costs were inflated to 2015 levels using the retail price index and were identified as ranging between £1,375 and £17,100 for the first year of blindness and £1,325 and £16,800 for each subsequent year thereafter. The most conservative estimate from the range identified was incorporated because of the uncertainty of the estimates as applied to glaucoma blindness. As such, a modest cost of £1,777 was used in the updated model to represent the economic burden of progression to visual impairment.

Sensitivity analyses were performed in order to examine how parameter uncertainty interacted with model outcomes(239, 240). Preliminary sensitivity analysis was performed at the earliest stages of model development in order to facilitate the understanding of how inputs interact with model outcomes. One-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were performed on the outputs generated by the Markov model once rationality in these outputs was assumed. From the derived ICERs, incremental cost-effectiveness planes were

constructed and from these cost-effectiveness acceptability curves (CEACs) were drawn indicating the probability of *proposed practice* being accepted at given levels of willingness to pay(26, 57).

Ethics approval for this modelling exercise was not required. Access to the non-identifiable patient data summarized in Table 1 was granted by the Caldicott Guardian at each participating centre. Subsequent analyses of the data, including that done in this work, were approved by a research ethics committee of City University London.

5.2 Results

5.2.1 Model Outputs

In total, 10,000 patients were simulated to enter into the health economic model with a positive cost differential of £298 per patient identified between *proposed practice* and *current practice* (Table 5-2). This implies higher costs with *proposed practice* but this corresponds with a positive utility differential (0.014 QALYS per patient). Consequently, an ICER of £21,392 per QALY was derived for *proposed practice*, a figure within the hypothetical NICE ceiling ratio of £30,000. Furthermore, a total of 785 visual impairment years were saved as a result of increased early monitoring associated with the *proposed practice* across the 25-year time horizon. These results are relevant to applying *proposed practice* to all newly diagnosed patients. Table 5-2 summarises the results for the scenarios when *proposed practice* is allocated to four specific subgroups of patients.

Table 5-2: ICERs produced once the proposed practice was provided to specific subgroups stratified by age and glaucoma severity.

Age Subgroup	Severity	Incremental	Incremental	ICER
All	All	£298	0.014	£21,392
Younger Patient	Early	£306	0.021	£14,797
	Late	£3,251	0.049	£66,219
Older Patient	Early	£287	0.014	£21,024
	Late	£4,170	0.030	£138,891

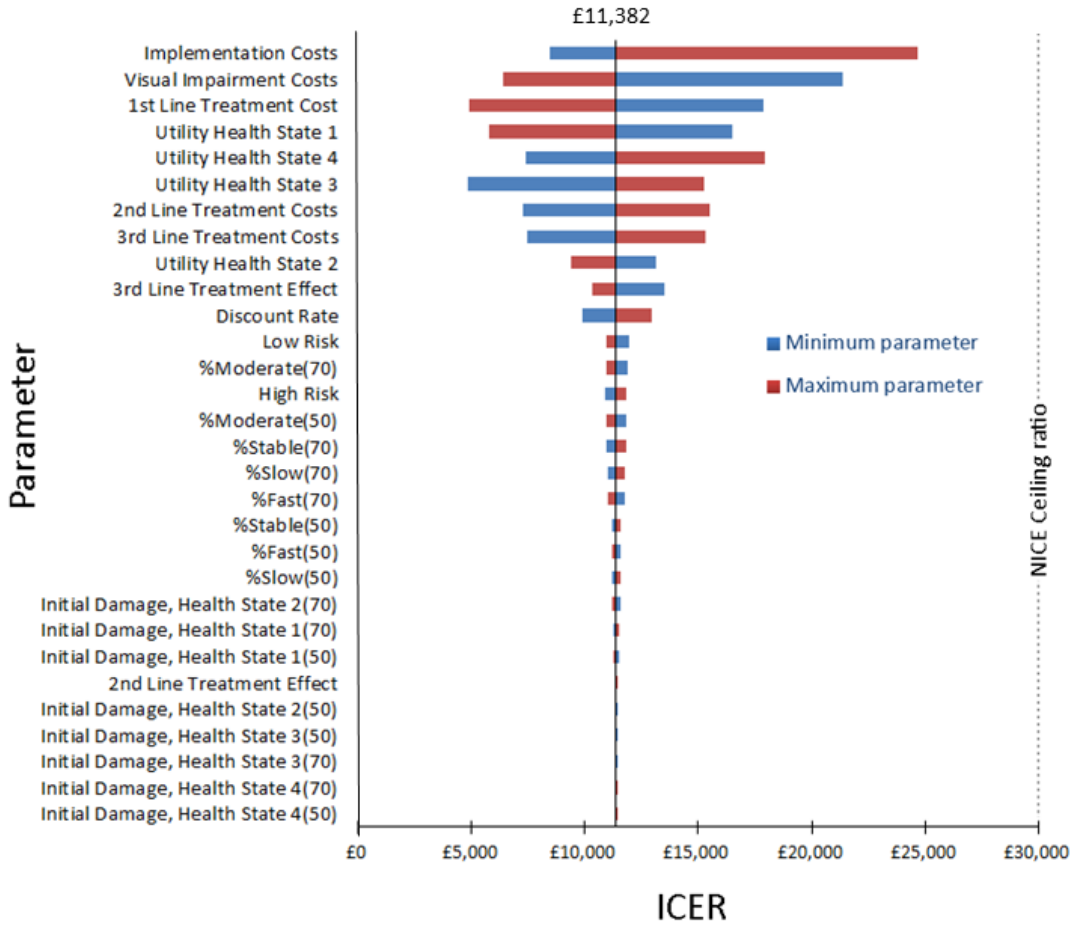
The best ICER associated with *proposed practice* was yielded from the younger cohort diagnosed with early (to moderate) stage VF loss in their better eye. Worse ICERs, incompatible with hypothetical willingness to pay thresholds, are returned for those patients that are already at an advanced disease state on diagnosis in their better eye.

After annual costs of visual impairment (£1,777 per year) were incorporated into the model, an incremental cost of £159 per patient (incremental utility of 0.14) was identified between *proposed practice* and *current practice.* There is no change in terms of incremental QALYs given that societal costs of visual impairment do not impact upon the patient themselves, so this yielded an ICER of £11,382 per QALY being derived for *proposed practice*. This represents a significant reduction in the ICER compared to results without visual impairment costs added. The latter were then varied to identify the threshold for cost neutrality between the *current practice* and *proposed practice* across both the full simulation. Under the full simulation, a value of £3,798 was identified as the required costs of visual impairment to equate *proposed practice* to *current practice*.

5.2.2 Sensitivity Analysis

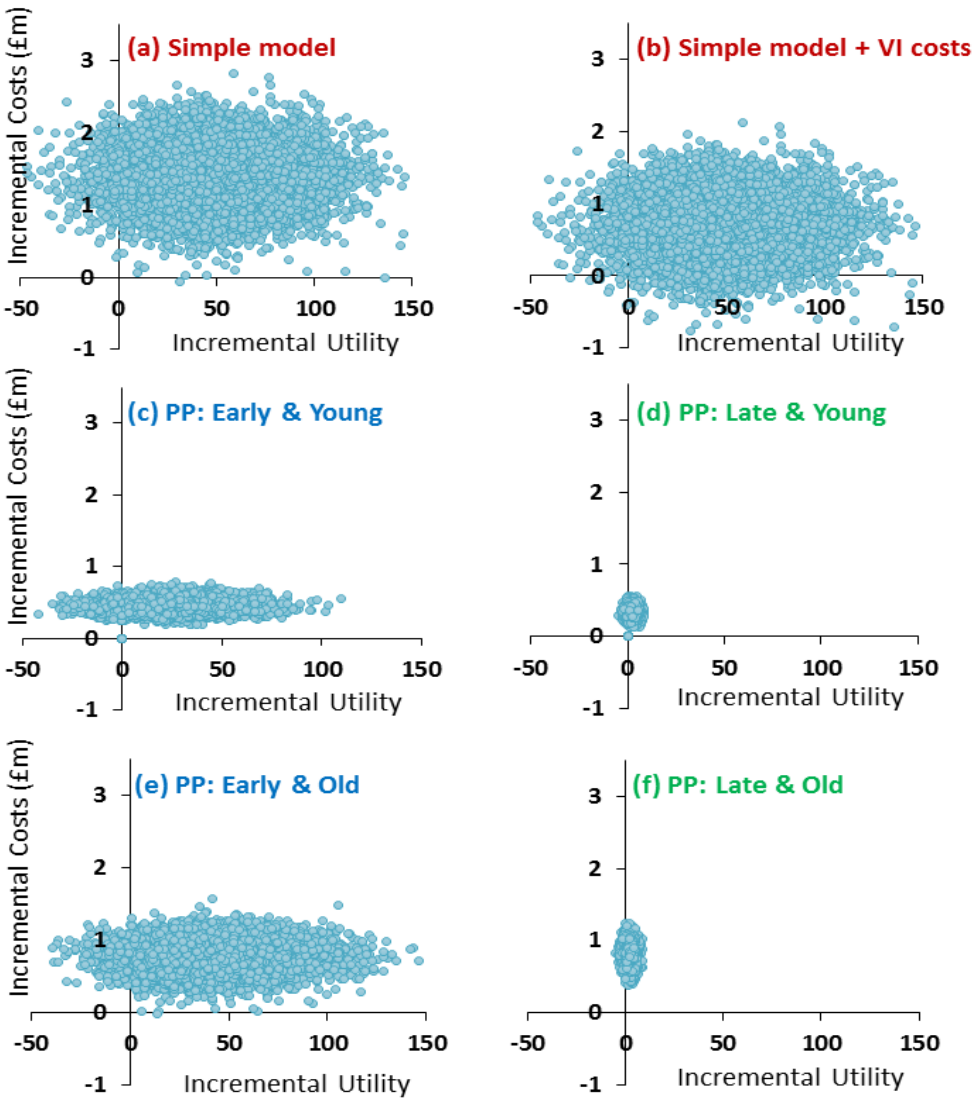
DSA results are presented in a Tornado diagram for the full simulation (Figure 5-2). The horizontal axis is the outcome (the ICER for allocating *current practice* to all newly diagnosed patients); along the vertical axis, parameters are ordered and horizontal bars represent the outcome range associated with the specified parameter's range (maximum and minimum value limits impact upon ICERs). For all parameters, outcomes were sorted in order of ICER impact. Uncertainty surrounding the implementation cost parameter and the visual impairment cost parameter resulted in the highest ICER variations but neither were sufficient to push the ICER beyond the £30,000 per QALY ceiling ratio. The next most important parameters were treatment costs and utility health states. Progression rates had little impact despite being varied by 10% in either direction.

Figure 5-2: Tornado Diagrams measuring the impact in variation in parameters for the health economic model with included visual impairment costs (ICER = £11,382). Maximum and minimum limits for parameters were identified. ICERs were derived and ordered in terms of impact (greatest to lowest ICER variation).



Unsurprisingly, in the PSA (see figure 5-3), greater cost-effectiveness was observed when costs of visual impairment were included (b) compared to when it was not (a). The observations in (b) are lower on the plane (indicating lower costs) with little change in the width of the observations (indicating similar effectiveness). *Proposed practice* in younger patients with early glaucoma (c), placed observations significantly lower on the plane than in the simple model (a), indicating a significant improvement on cost-effectiveness. Patients (both young and old) with advanced glaucoma yielded a compressed cluster of observations. Simply, the model is inferring that those with late glaucoma have less vision to save; therefore, less incremental utility can be derived. For older patients with early glaucoma (e), observations were more spread across the cost-effectiveness plane suggesting greater likelihood of utility gain given their greater preserved vision.

Figure 5-3: Cost-Effectiveness Planes for the different subgroups analysed.



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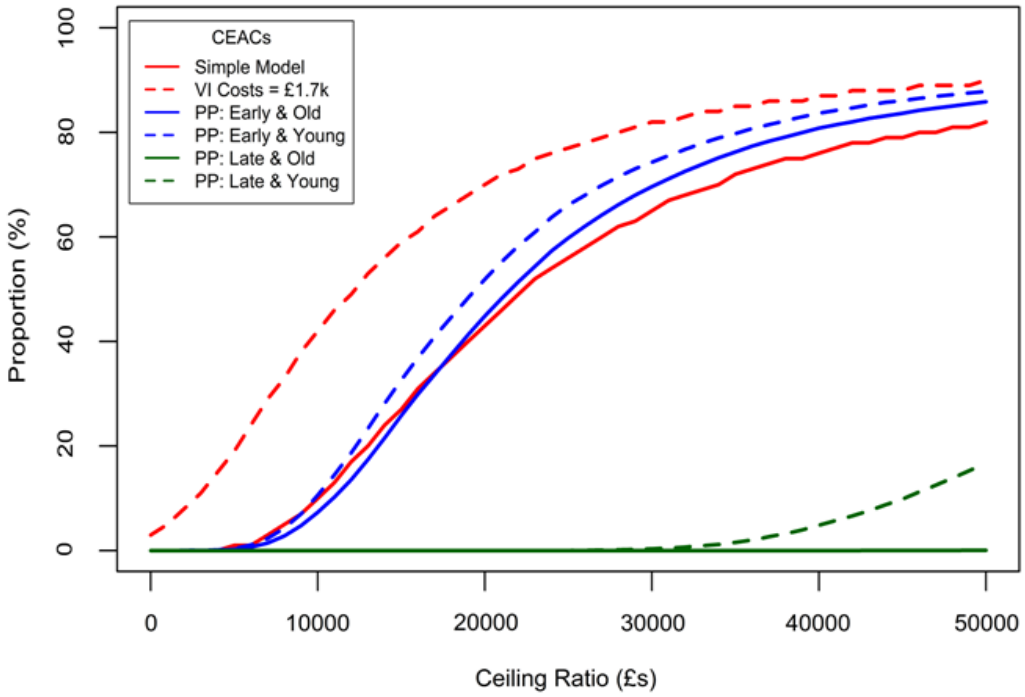
effectiveness plane suggesting greater likelihood of utility gain given their greater preserved vision.

Figure 5-4: Cost Effectiveness Acceptability Curves across the subgroups analysed.



CEACS were derived from these simulations (see Figure 5-4). Willingness to pay for each QALY gained was varied from £0 to £50,000 and the proportion of simulations deemed acceptable at this level were recorded. Similar shaped CEACs were observed for the model with and without the visual impairment costs added. However, the shift of the CEAC to the left for the model with visual impairment costs included indicates an increased probability of acceptance of this scenario. At the £30,000 per QALY ceiling ratio, the proposed practice was acceptable 82% of the time when these indirect costs were modelled whilst only 65% of the time when they were not. When *proposed practice* was provided to patients with early glaucoma, there was less deviation from the simple model with 70% (old) and 74% (young) being observed to be acceptable at the £30,000 per QALY ratio. CEACs trail close to zero for the patients diagnosed with late disease indicating a significant lack of cost-effectiveness likelihood for these subgroups.

5.3 Discussion

This modelling exercise primarily sought to examine whether increased VF monitoring at the earliest stages of disease identification in COAG (i.e. six VFs in the first two years after diagnosis) would be cost-effective compared with the assumed *current practice* of one VF per year. An ICER of £21,392 indicates that the *proposed practice* is a cost-effective strategy for all patients given a hypothetical £30,000 per QALY NICE acceptability ceiling ratio. So these health economic findings support the EGS guideline recommendation of undertaking 6 VFs in the first two years after glaucoma diagnosis.

Introduction of costs of visual impairment further increased the cost-effectiveness of the *proposed practice* to £11,382. A cost of visual impairment threshold of £3,798 per year was identified as the minimum value required ensuring that the *proposed practice* would equate to *current practice* in terms of costs across the full 25-year time horizon of the model. Put another way, if cost of visual impairment per year is assumed to be greater than £3,798 per year then, *proposed practice* is preferable to *current practice*. This figure sits at the lower end of the distribution of the costs estimated in the Meads et al. study (£1,325 to £16,800 per year throughout the duration of patients residual lifetime)(135). Moreover, other studies have estimated costs of visual impairment to be significantly greater. For example, Lafuma and colleagues reported a value of €13,674/year in the UK in 2006 (equating to about £11,000/year when inflated to 2015 values and converted to pound sterling) and Burr et al. suggested the figure could be as high as £40,000/year(136, 237). Therefore, if the values found in these alternative studies were used, the *proposed practice* would be the cheaper long-term patient pathway compared to *current practice* due to the costs saved by reducing the amount of patients progressing to visual impairment over the 25 years. Moreover, this report should stimulate more research into the hidden costs of burden of sight loss and encourage other researchers to include them in their health economic models when studying conditions that lead to sight loss and to investigate further. For instance, 'hidden' costs arise because people with visual impairment tend to have longer hospital stays for co-existing morbidities (241, 242) whilst risk of falling is higher for the visually impaired, inevitably leading to more 'hidden' costs(243).

Within this modelling exercise, patients were loosely defined to be in a severe disease state if the MD is worse than -12dB in the better eye. This threshold is not entirely arbitrary because it approximately equates to a patient failing the VF component of legal

fitness to drive in the UK(113) and has been used in staging disease severity in COAG before. In those patients with VF loss better than this threshold, proposed practice seems particularly cost-effective. Patients with sight loss worse than this threshold would likely be on maximum therapies anyway and the model suggests it would be less cost-effective to monitor them closely at the outset. This might appear controversial but it simply reflects the limited treatment options in late stage glaucoma. Interestingly the idea that surgery ought to always be the primary treatment option for people diagnosed with advanced glaucoma is being tested in an on-going large randomised trial in the UK (https://www.tagsstudy.co.uk/).

This study found that the *proposed practice* is more cost-effective in younger patients (see Table 5-2). This is unsurprising because the costs of *proposed practice* are more likely to be recovered for a person with longer residual life expectancy, with the economic argument of early investment in preserving future vision. More intensive monitoring of these patients is obviously worthwhile in order to establish speed of loss and improve their clinical management. Yet findings within this thesis indicate that frequency of monitoring in clinics in England does not vary by the age of the patient (or rate of loss or disease severity for that matter) - younger and older patients simply get the same diet of VF testing (see Chapter 4, Figure 4-5). Therefore, and at the very least, the model provides evidence for the potential cost-effectiveness of stratifying patients to more or less monitoring and this is an important conclusion from this work. A prospective research study examining this issue is recommended. At the moment, there is a tendency to have a 'one size fits all' approach to monitoring the diagnosed patients and this is likely a suboptimal method for monitoring large cohorts of patients.

Sensitivity analysis identified implementation costs as the most important parameter impacting upon the ICER, resulting in ICERs ranging from £8,400 per QALY at its minimum value to £24,700 per QALY at its maximum value. A full costing study examining the range of values is clearly required to truly ascertain whether this maximum value is accurate or if there is already sufficient excess capacity to allow for the *proposed practice* (the minimum modelled assumption). The second most important parameter within the sensitivity analysis was the costs of visual impairment. The minimum assumption of costs to society equalling £0 resulted in a maximum ICER of £21,400. However, this perceived minimum limit is unlikely to be representative in the real world especially given the negative externalities associated with glaucoma. The message about the need for further

studies to estimate these costs more precisely is therefore reiterated(237); without them the predictions from health economic models of age-related eye disease will always lack precision. Costs associated with the 1st line of treatment modelled within this study were identified as the third most important factor within the Tornado analysis with the lowest assumed value (£389) resulting in an ICER of £17,800. As *proposed practice* accelerates the time it takes to get an 'upgrade' in treatment modality provision, patients are therefore moved away from the 1st line of treatment at an increased rate. If costs for the 1st line of treatment are relatively low, it becomes less economically efficient to move to the 2nd and 3rd line of treatment, therefore making the *proposed practice* less cost-effective. This result points to the need for better data on true costs of treatment for glaucoma and this is worthy of further research.

5.3.1 Limitations of the study

It is difficult to accurately model real world clinical decision making. Here clinical decision pathways were developed in consultation with two practicing glaucoma specialists. Decision making varies from clinician to clinician however and it is possible that a clinical review panel made up of different ophthalmologists could have resulted in alternative decision nodes being constructed. In addition, three possible treatment lines only were implemented for simplicity but in reality there are significantly more possible variations in treatment lines that the patients could undergo.

Critically this model does not consider the effect of false positive decisions on VF progression. After all, it has been shown that increasing VF testing will inevitably affect specificity(175). Therefore, with *proposed practice* patients may receive intensified treatment when it is not required and the model is not adjusted for this cost. The model also assumed the VF changes in a linear fashion only. This is reasonable given work done in this area(244) but deterioration to noticeable binocular vision loss may be more suddenly noticed in patients(245).

An economic evaluation using discrete event simulation might also model the process more accurately and this has been used elsewhere(164). Still, such models are complex and difficult to interpret and a Markov model structure offers simplicity and transparency. The model structure is likely also limited by the way in which disease severity was categorised - more work is needed to establish meaningful stratification of

functional loss in glaucoma. These results only considered a summary measure from the VF. Research has shown that an index like MD does not capture location and spatial extent of VF loss in patients(245). For example, two patients with the same MD might have different visual function. Moreover, there is debate about using a measure of binocular VF loss and aligning this with utilities(104, 106). Finally, the model does not capture the co-morbidities of patients; this could be concomitant eye disease or other chronic conditions.

5.3.2 Future Research

Measuring impact of visual function loss on quality of life requires further study in order to test the clinical- and cost-effectiveness of health service delivery of COAG(111). Further research to quantify the costs of sight impairment is also a priority. Also, little is known about how patients adapt to gradual sight loss in glaucoma and this subject is worthy of further study; This could have a significant bearing on estimating utilities in health economic models for COAG(181). Indeed it could be suggested there are clear uncertainties surrounding the utilities in these models despite exemplar studies attempting to derive meaningful values(161). New research should look at the precision and accuracy of these values. Furthermore, whilst a range of 'theoretical' implementation costs were examined in the sensitivity analysis of model results, it was beyond scope to examine in detail the costs associated with implementing *proposed practice;* this clearly ought to be the subject of further research along with consideration of the thoughts on increased testing of patients and clinicians(206, 232). Consideration of innovative and affordable health service delivery redesign is likely to be a wider debate that needs to be addressed too, as has been recently suggested for people with ocular hypertension(246).

5.4 Conclusion

Results from this modelling exercise indicate the health economic benefits of intensifying monitoring of patients after they have been newly diagnosed with COAG. Increasing the number of VF examinations to better determine those patients' that are rapidly losing vision appears to be cost-effective; this might be particularly true for younger patients. A study on the resource implications for glaucoma follow-up and costs of sight impairment

from COAG would be worthwhile. A prospective study of different follow-up patterns, especially stratified among different patient groups is recommended.

Chapter 6: Conclusions

Whilst a considerable amount of research has taken place examining how best to identify, treat and monitor glaucoma patients, there is little existing literature examining guidelines for glaucoma service provision from a health economic perspective. Whilst maximisation of patient outcomes represents a key objective with the UK NHS, there has to be a consideration of the costs derived in order to achieve them. This is especially the case given the finite nature of the financial resources that are used to produce the outcomes. Given the zero-sum game associated with taxation only based funding structures, the provision of resources for one strategy requires that resources are less readily available to finance other strategies. It is therefore imperative that budget holders are provided with sufficient information so as to choose the treatment and management strategies that represent the best value for money. This thesis and the studies contained within it seeks to use real world clinical data in combination with health economic principles to examine suggested monitoring guidelines for glaucoma whilst also attempting to establish the trends associated with service provision to establish whether improvements are being made. Below, I summarise the findings of the five thesis chapters and the conclusions drawn from them before summarising the novel contributions of the thesis and describing further questions and study arising from this research.

6.1 Summary

The study described in Chapter 2 investigated the cost-effectiveness of undertaking 6 VFs in the first two years in order to expedite the identification of those patients most likely to progress to a state of visual impairment within their lifetimes. A health economic model was constructed to compare this proposed practice against the current practice of annual VF testing. The health economic model found that it would be cost effective to undertake this increased monitoring strategy under NICEs hypothetical cost-effectiveness ceiling ratio although further research was required to assess the costs of the extra infrastructure that would be required to implement such a strategy. Furthermore, greater understanding of how health state utility is quantified in glaucoma

is required as the parameters used in the study were found to potentially impact upon the assessment of cost-effectiveness.

The study in Chapter 3 examined the distributions of existing health states in greater detail by retrospectively analysing VF data sourced from around England. The study also examined the trends associated with the degree of severity at presentation over time in order to assess whether detection is improving over time. It was observed that there was moderate evidence that glaucoma patients were being detected earlier over time however a key finding of the study was that too many glaucoma patients begin treatment once the irreversible disease has already progressed to an advanced stage in at least one eye.

The study described in Chapter 4 retrospectively investigated rates of VF progression in England in order to identify whether rates of disease worsening is getting better over time given the improvements in treatment techniques that have occurred periodically. The study in this chapter also investigated the distribution of rates and the frequency of patient follow up stratified by age and severity of loss at baseline to expound on how rates and monitoring can vary by patient characteristics. It was observed that rates were improving over time, however the average rate of improvement was small and there was no reduction in the proportion of rapidly progressing eyes over the decade examined. The study also confirmed the wide belief that that older eyes and those eyes with greater disease severity progressed at a more rapid rate whilst the study also found that the frequency of monitoring of the VF did not vary by likelihood of progression to visual impairment.

The study in Chapter 5 represented and update of the model constructed in Chapter 2 to incorporate the more detailed findings of Chapter 3 and Chapter 4 in terms of existing health state distributions and stratified progression rates respectively. The model was also updated to account for the societal costs associated with glaucoma in order to count the true total costs associated with the condition. The cost-effectiveness of increased monitoring at the earliest stages of identification was found to increase as the indirect costs of visual impairment were incorporated into the model even when updates to the distributions of existing damage and progression rates were implemented.

6.2 Further work

6.2.1 Illness Perception in Glaucoma Study (IPIG)

As previously discussed, cost-effectiveness evaluation has sought to further the understanding of efficiency in visual health by synthesising data on utility and costs through the processes of cost effectiveness analysis(63, 164). In order to quantify incremental benefit, subjective assessments of improvements in quality of life are required. These assessments are often represented by non-patients valuing the utility of these improvements. Non-patients therefore often determine which drugs and interventions are funded and provided by the NHS in the UK.

Existing methods of utility quantification are being increasingly questioned however. There is evidence to suggest a disparity exists between how non-patients predict life would be like with a condition compared against patients' actual experiences. In a study of 80 patients against 80 non-patients, Walsh et al. found non-patients to predict that life would be worse with a health state than patients actually report(185). These disparities in judgment were reasoned due to non-patients failing to take into account that patients adapt to living with a health state, a supposition supported by other academic literature(247-249). This could potentially result in non-patients failing to accurately anticipate the preferences of patients when valuing the utility of quality of life improvements.

Furthermore, in another study examining the relationship of the quality of life associated with visual disability from glaucoma, Odberg et al. studied the patient perception of glaucoma identified through questionnaire responses(184). Of the 589 questionnaires studied, 80% of subjects reported negative emotions at diagnosis, 31% were found to be afraid of going blind whilst 46% reported that they had not detected any issues with their visual function prior to their glaucoma diagnosis. It was consequently argued that the diagnosis of glaucoma itself reduces quality of life of the patient despite only half of those studied experiencing any problems with their visual function. This discontinuity between patient perceptions and self-reported quality of life implies that negative emotional perceptions of the condition glaucoma can potentially outweigh the impact on visual function itself. This suggests non-patients are perhaps not sufficiently qualified to provide insight into how glaucoma should be prioritised.

There are therefore two main issues with how quality of life is investigated in glaucoma. Firstly, that non-patients lack the knowledge that patients are able to adapt to their conditions over time. Secondly, that both patients and non-patients are potentially negatively affected by a diagnosis of glaucoma itself given the negative emotional representations associated with the condition. To investigate these issues in greater depth, two studies are currently planned: the Illness Perception in Glaucoma: case–control study (IPIGa) and the Illness Perception in Glaucoma: non-patient study (IPIGb).

6.2.2 IPIGa: Methods and Materials

The IPIG case-control study looks at real patients diagnosed with COAG or OHT and compares the emotional representations of those with a new diagnosis compared to those that have had their diagnosis for at least two years. The primary aim of this study is to assess the negative impact of the actual 'diagnosis' of COAG or OHT upon perceived quality of life. This is important because prognosis in most patients with these chronic conditions is actually quite positive, with the majority of patients not reaching a significant level of visual disability within their lifetime(153). This has implications about how 'diagnosis' of glaucoma is communicated in a clinical setting. Furthermore, the health economic values placed on chronic conditions are inherently linked to its illness perception. This study intends to show that this illness perception is 'dynamic' in glaucoma; different outcomes could be obtained depending on the time that has passed since diagnosis. Health economic measures such as QALYs are derived from assessment of health states using a complicated calculation which weighs the cost of a treatment against its benefit, this study therefore aims to examine the accuracy of such metrics.

6.2.3 IPIGb: Methods and Materials

Following on from the IPIG: case-control study, The IPIG: non-patient study will examine the impact comprehension of glaucoma has on the perception of glaucoma by respondents with self-reported healthy visual function. As previously discussed, non-patients are often used in the assessment of quality of life to establish priority of access to resources. In addition, they are also being used to compare intervention effectiveness for health economic cost effectiveness analyses such as those undertaken in Chapter 2

and 5 of this thesis. It has however already been shown that non-patients overestimate the impact a glaucoma diagnosis would have upon quality of life. The aim of this study therefore is to illustrate the role knowledge of the characteristics of the disease plays when quantifying potential impacts.

6.3 Thesis contributions

Overall, there are various contributions to the field that have resulted from this thesis:

- The thesis has tested the health economic implications of undertaking the EGS guidelines of performing 6 visual fields in the first two years to better identify those patients most of risk of visual impairment in their residual lifetimes (Chapter 2)
- The thesis has established estimates using real world clinical data for the severity of vision loss at diagnosis in glaucoma patients in England (Chapter 3).
- The thesis has examined and identified the rates of which improvements in glaucoma identification in England has been taking place over time (Chapter 3).
- The thesis found that a significant proportion of patients are presenting to glaucoma care services in the UK in the first instance with significantly progressed VF damage (Chapter 3).
- The thesis has investigated to see whether rates of visual field progression in England has been improving over time and whether improvements in disease progression are being observed in those patients at most risk of suffering from visual impairment in their lifetime (Chapter 4).
- The thesis has provided confirmation that older patients and those with the most advanced stages of disease are most likely to progress at faster rates of deterioration (Chapter 4).
- The thesis has established that frequency of follow up does not vary by age, disease severity or by rate of progression, suggesting that little focus is being placed on those most at risk patients (Chapter 4).
- This thesis found that the implementation of the EGS guidelines would be most cost-effective if targeted specifically at younger patients and those at earlier stages of disease severity (Chapter 5).

Chapter 7: References

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