DOCTOR OF PHILOSOPHY

Requirement for and optimisation of premium intraocular lenses

Gurpreet Bhogal

2012

Aston University

REQUIREMENT FOR AND OPTIMISATION OF PREMIUM INTRAOCULAR LENSES

GURPREET KAUR BHOGAL

Doctor of Philosophy

ASTON UNIVERSITY

September 2012

ASTON UNIVERSITY

REQUIREMENT FOR AND OPTIMISATION OF PREMIUM INTRAOCULAR LENSES

GURPREET KAUR BHOGAL

DOCTOR OF PHILOSOPHY

SEPTEMBER 2012

Summary

Premium intraocular lenses (IOLs) aim to surgically correct astigmatism and presbyopia following cataract extraction, optimising vision and eliminating the need for cataract surgery in later years. It is usual to fully correct astigmatism and to provide visual correction for distance and near when prescribing spectacles and contact lenses, however for correction with the lens implanted during cataract surgery, patients are required to purchase the premium IOLs and pay surgery fees outside the National Health Service in the UK. The benefit of using toric IOLs was thus demonstrated, both in standard visual tests and real-world situations. Orientation of toric IOLs during implantation is critical and the benefit of using conjunctival blood vessels for alignment was shown. The issue of centration of IOLs relative to the pupil was also investigated, showing changes with the amount of dilation and repeat dilation evaluation, which must be considered during surgery to optimize the visual performance of premium IOLs.

Presbyopia is a global issue, of growing importance as life expectancy increases, with no real long-term cure. Despite enhanced lifestyles, changes in diet and improved medical care, presbyopia still presents in modern life as a significant visual impairment. The onset of presbyopia was found to vary with risk factors including alcohol consumption, smoking, UV exposure and even weight as well as age. A new technique to make measurement of accommodation more objective and robust was explored, although needs for further design modifications were identified. Due to dysphotopsia and lack of intermediate vision through most multifocal IOL designs, the development of a trifocal IOL was shown to minimize these aspects.

The current thesis, therefore, emphasises the challenges of premium IOL surgery and need for refinement for optimum visual outcome in addition to outlining how premium IOLs may provide long-term and successful correction of astigmatism and presbyopia.

Keywords: presbyopia, accommodation, intraocular lens, pupil centration, astigmatism

Dedicated to my late grandfather

Jagir Singh Bhogal

Acknowledgements

Foremost, I would like to express my gratitude to my supervisors Professor James Wolffsohn and Dr Leon Davies for inspiring me to pursue a career in research and mostly for providing me with the opportunity to begin this career in ophthalmic research. Their expertise and advice have been invaluable throughout the course of this doctorate and I have been highly privileged to have worked with such supportive and knowledgeable supervisors.

I am grateful to Aston University and the Ophthalmic Research Group Anterior Eye team for supporting this research. Many thanks to Pickford Opticians for kindly providing a provision for conducting my research in addition to the substantial contributions to data collection.

I would also like to acknowledge and thank my colleagues Dr Phillip Buckhurst, Dr Amy Sheppard, Dr Stephanie Mroczkowska and Professor Sunil Shah for their individual contributions to data collection and Dr Tom Drew and Alec Kingsnorth for their advice and development of the electronic accommodometer. Thanks also to Dr Hannah Bartlett and Dr Mark Dunne for their statistical expertise.

Finally, I give special thanks to all my family and friends for all their kindness and support. Thank you to my fiancé, Gurjeet Bhamra, who has been a pillar of strength throughout my studies. I owe sincere thanks to my mother, father and brother Charanpreet for their support, unconditional love and continuous encouragement in all my life goals. To my father especially I would like to say thank you for encouraging me to follow a career in optometry and thank you to my grandparents for their heartfelt blessings. I am forever grateful to you all.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

Introduction

Cataract, or clouding of the crystalline lens in the eye, is currently the leading form of visual impairment in the world and surgery to remove cataracts is now the most common surgical procedure in the developed world, undertaken by ophthalmologists. Cataract Surgical Rate (CSR), defined as the number of cataract extractions carried out per million population per year is estimated at 4,000-6,000 within developed countries (Vision 2020; Sparrow, 2007). The demand for cataract extraction and intraocular lens (IOL) implantation has grown due to improvements in the healthcare provision, which has increased life expectancy (Foster, 2000). In addition, visual expectation and task demands are increasing within the older population, particularly with the demands of mobile communication. Since the advent of intraocular lenses (IOLs) in the 1950's, designs have advanced to not only optimize the spherical power of the eye for distance vision, but also aim to achieve spectacle independence through correction of astigmatism and by increasing the range of clear focus in the presbyopic eye. These 'premium IOLs' are not normally covered by public health systems and may benefit patients more than lenses that are conventionally implanted during cataract surgery. Hence a clear evaluation of the benefits they offer and when they should be considered needs to be understood.

1.1. Crystalline Lens

The crystalline lens (*Figure 1.1*) is an avascular, biconvex structure located in the posterior chamber of the eye between the posterior surface of the iris and anterior vitreous chamber, composed of 65% water and 35% protein (Pipe and Rapley, 1987).

It is a flexible structure and can change shape by forces of contraction by the ciliary body and zonular fibres that are attached to the lens. This creates a change in dioptric power of the lens known as accommodation, allowing near objects to be focused on the retina. The lens provides approximately 20 dioptres of refractive power in its non-accommodated state and contributes to a third of the overall refractive power of the eye.

Aston University

Illustration removed for copyright restrictions

***Figure 1.1**: Crystalline lens*

The crystalline lens is initially formed from the inverted epidermal layer and is known for constant cellular mitosis; as more cells are produced older cells are pushed towards the centre of the lens leaving newer cells in the periphery (Davson, 1990). The cells eventually lose all their organelles giving the vital property of transparency.

The thickness of the lens in the un-accommodated state is approximately 3.5-5mm, which increases by 0.02mm throughout each year of life (Dubbelman *et al.,* 2001; Remington, 2005). The diameter of the adult lens measures approximately 9mm (Hogan *et al.,* 1971; Remington, 2005) which increases through life from 6mm, with its posterior surface being much steeper in comparison to its anterior surface.

The lens is attached to the ciliary body by elastic fibres known as the zonules of Zinn. The structure consists of many components (*Figure 1.1 &1.2*) but is often divided into three main entities; the lens capsule, lens fibres and epithelium. The lens capsule is an ellipse shaped basement membrane that surrounds the lens cortex and nucleus. It is the thickest basement membrane within the human body and comprises of two main purposes; firstly it encases the lens contents and IOLs when implanted and secondly translates the force of contraction to the lens components during accommodation. Additionally, the capsule provides a barrier to large molecules from entering into the lens which would obscure its transparency.

The main component of the capsule is type IV collagen arranged in a meshwork with sulphated glycosaminoglycans giving its property of elasticity. The young lens capsule is very strong and shows high elasticity which is eventually lost with aging (Krag *et al.,* 1997). The thickness of the capsule is not uniform; it is thickest around the anterior pole and thinnest at the equator. The lens capsule comprises of the anterior and posterior capsules which merge at what is known as the ‘equatorial’ plane (David *et al.,* 2007) and is often described as being axisymmetric (David *et al.,* 2007; Krag *et al*., 1994), showing nonlinear behaviour (David *et al*., 2007; Krag *et al.,* 1994).

Aston University

Illustration removed for copyright restrictions

Figure 1.2: *Internal view of crystalline lens*

There is rising interest in the functioning of the capsule as such knowledge provides a wider understanding of the mechanism of accommodation. Pedrigi *et al* (2007) suggest cataract extraction may cause alterations to the properties of the lens capsule and it has been established there is an increase in lens capsule thickness following cataract extraction, possibly due to deposition of proteins such as, collagen types I and III. Such interference in the structure of the capsule may enhance the development of posterior capsular opacification (PCO).

Fincham (1937) first described the elastic properties of the lens capsule, as he noted the remaining lens adopted an un-accommodated state on removal of the capsule, suggesting the capsule moulded the lens substance into its accommodated shape. Since then it has been confirmed that both the lens material and lens capsule indeed possess some elastic properties (Weale, 1963).

The lens fibres which make up the cortex and nucleus of the lens are continually produced all through life, with newer fibres being laid on the outer regions of the lens. These crescent-like shaped cells measure approximately 8-10nm. Within the cytoplasm of these fibres, lens proteins called crystallins are found in high concentration. Crystallin concentration in the nucleus is approximately 70% and 15% within the lens cortex, giving the crystalline lens a gradient refractive index (Weeber *et al.,* 2005).

The epithelium of the lens, located immediately adjacent to the anterior lens capsule, is composed of a single layer of cuboidal cells providing metabolic transport for the entire structure and regulating its osmolalrity, in addition to providing new lens fibres through division and differentiation. These cells span 15µm in width and 6µm in height and become much longer towards the lens equator (Pipe and Rapley, 1987).

Within the pre-equatorial region of the lens, known as the germinal zone, cell mitosis regularly occurs, the new cells then move into a transitional zone where they differentiate into lens fibre cells. The processes of the new cells pass through the anterior and posterior epithelium, forming layers on top of older cells by pushing older fibres towards the nucleus of the lens. These processes are the lens fibres. The fibres eventually meet with other fibres within their layer and form a suture. During embryological stages they link as three branches forming a Y-shaped suture which further develop into a radial pattern as seen in an adult lens.

The crystalline lens receives nutrients from the aqueous humour and vitreous via diffusion through the lens capsule with waste products being removed in a similar way, generally there is a low metabolic requirement.

Measurements of capsular thicknesses between ages 1 to 94 years show increases in thickness up to 70 years (Krag *et al.,* 2003) although this differs between the anterior and posterior regions. The posterior capsule shows no changes with age and may even become thinner with age (Barraquer *et al.,* 2006), whereas the anterior capsule is considerably thicker (Bron *et al.,* 1997) and is the thickest of basement membranes in the entire human body (Strenk *et al.,* 2005).

Understanding the mechanism of functions of the lens and its components and the extent to which they contribute to the phenomenon of accommodation will allow further advances in creating more efficient IOLs with the capability to provide effective accommodation or reviving accommodative ability.

1.2. Accommodation

Accommodation is the ability to alter the dioptric power of the eye by changes in anatomical structures in order to produce a retinal image of objects at various distances. Many theories have been postulated to explain this phenomenon but its exact mechanism has not yet been determined. The first comprehensive and most widely accepted theory of accommodative mechanism is that of Helmholtz (1855, cited in Strenk *et al.,* 2005), whereby accommodation results from ciliary muscle contraction, causing relaxation of resting zonular tension surrounding the lens equator. The outward tension on the lens capsule is hence released leading to an increase in anterior and posterior lens surface curvature with a decrease in lens diameter, resulting in an increase of the dioptric power of the crystalline lens. Cessation of accommodation is facilitated by relaxation of the ciliary muscle, zonular tension is restored on the lens equator, pulling the capsule into a flatter form, decreasing the curvature of lens surfaces and increasing the lens diameter (Helmholtz 1855 cited in Strenk *et al.,* 2005).

The Helmholtzian theory suggests the crystalline lens is an elastic entity taking on a natural accommodative state with removal of tension forces. The theory was based upon observations of forward movements of the anterior lens surface and increases in curvature with accommodative effort, it was also believed that the posterior surface curvature increased but no movement was observed. Axial thickness was recorded to have increased by 0.5mm, however, as the lens volume did not alter it was concluded that equatorial diameter may decrease on accommodation.

In order to refine the Helmholtzian theory, experimental work by Fincham (1937) recognized the backward movement of the posterior lens surface, in addition to ciliary body movement and decreases in lens diameter. It was soon concluded that the lens capsule is under tension whilst unaccommodated which is released on accommodative effort, providing evidence for Helmholtz previous description.

Despite evidence from Fincham, Helmholtz theory did not gain entire acceptance and has faced many opposing theories. One opposition, prior to Fincham's findings, includes that of Tscherning (1895, cited in Strenk *et al.,* 2005) who believed the zonular fibres do not relax and contraction forces of the ciliary muscle further increased zonular tension moulding the lens into a conoidal shape. However, Fincham (1937) later provided evidence that the zonular tension in fact decreases on accommodation, hence proving the theory of Tscherning incorrect. A second theory proposed by Tscherning (1909, cited in Strenk *et al*., 2005) explains ciliary contraction to exert tension on the choroid which compresses the vitreous against the periphery of the posterior lens surface whilst the anterior lens surface remains stationary with tension from zonular fibres.

A more recent theory by Schachar *et al* (1992), in favour of Tscherning, proposes stretching of the lens causes the central lens surface to become steeper and central thickness to increase while peripheral areas of the lens surface become flatter inducing an increase in power. Schachar and Anderson (1995) provide details that movement of the anterior ciliary muscle towards the sclera, on contraction of the ciliary muscle, produces increased zonular tension at the lens equator while tension is released from anterior and posterior zonular fibres. It is believed that the outward force produced shifts the lens equator towards the sclera which with relaxation of zonules would reduce the curvature of peripheral lens surfaces coupled with increases in central curvature. Schachar's theory however has not gained wide acceptance. There has been controversy over Schachar's proposals as various studies have failed to support his theory of accommodation, also studies of scleral expansion surgery have not reported any valuable restoration of accommodation (Glasser and Kaufman, 1999; Mathews, 1999).

Obtaining in-vivo evidence for accommodation theories is challenging as imaging of the ciliary body and fibres are obstructed by the iris as well as image distortion with corneal power (Strenk *et al.,* 2005). Published observations by Fincham (1937, cited in Strenk *et al.,* 2005), however, on a case of aniridia noted a decrease in diameters of the lens equator and ciliary body with increases in lens thickness. Fincham's finding has been further supported by more recent work of Wilson (1997), where retro-illumination infrared video imagery has also captured a decrease in lens equator diameter.

The general understanding of accommodation at present combines the findings of Helmholtz and Fincham. On accommodation, contraction of the ciliary muscle causes movement towards the lens equator releasing zonular tension. The lens capsule then shapes inner softer material into its accommodated form. Such an action increases lens surface curvatures and axial thickness with a corresponding decrease in diameter. Ceasing accommodation involves relaxation of the ciliary body which is pulled backwards. Zonular fibre tension is then restored pulling the lens back into a flatter form.

1.3. Presbyopia

The progressive loss of accommodation with age, termed presbyopia, is a process believed to occur as a result of age-related anatomical changes of the eye. Although, not yet entirely understood, it is assumed to be resultant of a variety of mechanical changes occurring within the accommodation system. Finding a solution to presbyopia is now becoming of growing interest in ocular research as visual demands of an aging population increase; for this the processes leading to presbyopia must be understood.

As with accommodation various explanations for the development of presbyopia exist. In periods of early research Helmholtz (1855, cited in Strenk *et al.,* 2005) had suggested it to be due to lens sclerosis whilst Donders (1864, cited in Strenk *et al.,* 2005) approached the explanation by describing the lack of shortening of the ciliary muscle with age. Further proposals by Tscherning-Pluugk (1909, cited in Strenk *et al.,* 2005) mention a reduction in viscosity of the vitreous humour (Strenk *et al.,* 2005). Proposed theories for presbyopia may be categorized as lenticular (Duane-Fincham theory) or extralenticular theories (Hess-Gullstrand theory).

It is generally assumed that presbyopia is a result of mechanical changes of the crystalline lens. For some time it has been assumed that increased stiffness of the crystalline lens is a cause of presbyopia development (Gilmartin, 1995) and has been supported by many investigators suggesting increased stiffness reduces the ability of the lens to change shape (Glasser *et al.,* 1998; Pierscionek, 1995; Atchison, 1995).

A more recent theory has been introduced proposing that lens growth leads to accommodative loss. With age the ciliary muscle is displaced anteriorly and inwards (Strenk *et al.,* 1999; 2005). The pupil margin is placed against the anterior surface of the lens which produces an upward force pushing against the iris and ciliary muscle. A second tangential force acts on the ciliary muscle produced by the sclera leading to an anterior and inward shift in the position of the ciliary muscle and iris root. Such displacement may cause a decrease in pupil diameter which may explain the development of senile miosis; this allows the pupil margin to move towards the anterior surface the lens where it is thickest. As lens growth continues with age, the ciliary muscle moves further anteriorly and upwards decreasing the circumlental space available and reducing the zonular tension in the process, thus creating greater curvature on disaccommodation with less effective ability to respond on accommodation. These events have been described as the Modified Geometric Theory which supports the variety of changes that have previously been indentified in lenticular aging (Strenk *et al.,* 2005).

Presbyopia is therefore most likely attributed to a combination of lenticular and extralenticular effects, making the condition ‘multifactorial’ (Weale, 1989; Burd *et al.,* 2002). However, the changes in mechanical properties of the lens structure do not present until after presbyopia has manifested. It may therefore be proposed that the continuous increase in lenticular mass generates these changes and is thus the sole factor for developing presbyopia. Presbyopia, although known to generally occur in the fourth decade of life, differs in rate of progression amongst individuals and may present earlier or later than when commonly expected. Various aspects of lifestyle may influence this rate of progression such as; diet, climate, latitude, environmental temperature and race. Understanding the aetiology of presbyopia will aid advancements in provisions which aim to correct presbyopia. In addition, knowledge of factors which increase or inhibit its progression will assist in the global research aim of alleviating this inevitable effect of age.

1.4. Cataracts

A cataract, from the Latin *cataracta,* is defined as opacification of the crystalline lens. It leads to the loss of transparency of the lens, causing vision to become hazy and if left untreated can eventually lead to blindness. Patients present with a reduction in visual acuity and occasional complaints of glare and 'clouded' vision.

Classification of cataracts may be anatomical or aetiological. Aetiological classification is divided into many different categories as listed in *Table 1.1*.

Aetiological Classification of Cataracts
Age-Related
Traumatic: injury or surgery
Congenital: hereditary or complications on birth
Systemic disease: diabetes mellitus
Secondary to ocular pathology: uveitis, glaucoma, retinitis pigmentosa
Drug-Induced: chloroquinine, steroids, amiodarone

Table 1.1: *Categories of aetiological classification of cataracts*

Age-related (senile) cataract remains the most common form encountered, however, the formation of a cataract can be multifactorial (Hammond, 2001) and cannot be attributed to a single aetiology. The anatomical classification seems the more suitable choice for clinicians, which consists of three types or categories; cortical, nuclear and subcapsular cataract, each of which impose a varied affect on visual function.

Cortical cataracts (*Figure 1.3.*) are opacities located in the lens cortex usually appearing as spokes radiating from the lens periphery. Such opacities rarely cause visual symptoms until they have extended further centrally interfering with the visual axis.

Figure 1.3: *Cortical Cataract*

Nuclear cataract (*Figure 1.4*) typically begins with brunescence, a brown discolouration, of the lens nucleus which increases central refractive index leading to its associated myopic shift.

Aston University

Illustration removed for copyright restrictions

Figure 1.4: *Nuclear Cataract*

Subcapsular cataract may occur on the anterior or posterior regions of the crystalline lens. Anterior subcapsular cataract occurs with fibrous metaplasia of the anterior epithelium whilst posterior subcapsular cataract (*Figure 1.5*) is due to migration of lens epithelial cells. Individuals suffer particularly debilitating glare from bright lights with the latter and often require removal far earlier than other forms of cataracts.

Aston University

Illustration removed for copyright restrictions

Figure 1.5: *Posterior Subcapsular Cataract*

If cataracts remain untreated they may progress into a mature cataract in which the crystalline lens becomes completely opaque. Over time leakage of fluid and shrinkage of the cataract leads to a hypermature cataract. Liquefaction of the cataract cortex into a milky fluid may result in morgagnian cataract; the lens nucleus in this case may sink inferiorly causing potential capsule ruptures. Leakage of fliud through ruptures may cause severe inflammation within the eye and may lead to phacomorphic glaucoma.

Cataract increases light scatter within the eye degrading contrast sensitivity (Elliott, 1993; Miyajima *et al.,* 1992) and as a result degrades the retinal image that is formed. There is currently no medicinal cure for the occurrence of cataract; the only successful remedy is surgical extraction and replacement of the natural crystalline lens with an intraocular lens implant (IOL).

Cataract extraction is indicated where there is significant deterioration of vision. It is generally agreed upon that referral for cataract surgery is warranted when visual quality is significantly affected. Referral for extraction, however, should not be based solely upon visual acuity measurements, degree of glare and ability to carry out daily tasks must also be taken into consideration. Individuals with reasonable acuity on high contrast test charts may demonstrate a reduction in visual functioning on contrast sensitivity or brightness acuity tests. No NICE (National Institute for Health and Clinical Excellence) guidelines currently exist on cataracts warranting referral for surgery hence symptoms must be appropriately investigated to determine how a patient’s lifestyle is affected by the reduction in vision.

1.5. Cataract Surgery

Cataract surgery dates back to early civilizations with the Egyptians, Chinese and Indus Valley civilizations all describing primitive methods of cataract extraction or displacement from the visual axis. A procedure known as couching was the earliest form of cataract treatment being dated as early as 600 BCE, this involved inserting a sharp needle into the eye and displacing the opaque material into the vitreous cavity, resulting in aphakia and blurred vision (Fan, 2005). Couching continued up to the 19th century and is still performed in some developing countries, however, severe post-operative complications are commonly associated with this procedure such as endophthalmitis and retinal detachment (Bamashmus, 2010).

Following the traditional couching method, intracapsular cataract extraction (ICCE) and extracapsular cataract extraction (ECCE) developed which coexisted in the early 1900s. ICCE, in which a large incision of approximately 14-16mm in the cornea facilitated the removal of the entire lens and capsule, this procedure however was associated with high rates of complications and is now rarely practiced. ICCE procedures require implantation of an anterior chamber IOL as it lacks the capsular bag to support a posterior chamber IOL, although the majority of cases remained aphakic, due to other factors such as anterior chamber depth.. Extracapsular cataract extraction (ECCE) involved removal of the cataractous material manually through a large incision of 10-12mm leaving the capsular bag within the eye and required stitches. These early procedures have now been superseded by the more preferred phacoemulsification procedure. Phacoemulsification works on a similar principle to ECCE where cataractous content is removed leaving the lens capsule behind, however removal is performed using an ultrasonic instrument to break up the cloudy material, allowing smaller incision sizes of approximately 3.2mm and fewer surgical complications. Due to the high costs of phacoemulsification ECCE is still commonly performed in developing countries and may occasionally be required in developed countries if phacoemulsification presents difficulty or to facilitate the removal of highly dense cataracts. As part of cataract surgery, intraocular lenses are usually implanted into the patient's eye to correct for the refractive error that would present with aphakia, relieving patients of significantly poor vision following surgery.

Prior to intraocular lenses, extraction of cataracts left patients aphakic requiring very high positive powered spectacles. Intraocular lenses to replace the optical power of the crystalline lens were not introduced until after the World War II. Sir Harold Ridley working in St. Thomas's Hospital in London examining aircraft pilots, with penetrating injuries from their shattered perspex canopes, noticed the relative biomimetic properties of the synthetic material (Apple and Sims, 1996). His early attempts at intraocular lens design and implantation required large corneal incisions and many failed due to optical and physiological complications, but formed the basis for the development of modern IOLs. Since then and with recent developments in intraocular lens implants there has been a growing interest amongst researchers in methods of restoring optimal vision following cataract surgery.

Before implantation, determination of IOL power is required, which is subject to various ocular measurements including; corneal curvature, axial length, anterior chamber depth and post-operative positioning of the IOL. Originally A-scan ultrasound and keratometry were performed; more recently pre-operative measurements are established using the Zeiss IOL Master, which utilises the sophisticated technique of partial coherence interferometry (PCI) to accurately measure axial length, anterior chamber depth and automated keratometry. Occasionally A-scan ultrasound is performed with more dense opacities due to measurement difficulties with PCI.

In recent years, with increased cataract extractions underway due to an ageing population, higher demands of spectacle independence from the older population have resulted and optimizing vision after cataract surgery is now paramount. Advances such as smaller wound incisions, continuous curvilinear capsulorhexis (CCC), improved biometric techniques and use of topical anesthesia have led to the highly successful post-operative outcomes of cataract surgery. As surgical techniques have advanced profoundly interests now turn to advancing intraocular lens designs to provide optimum vision following cataract extraction.

1.6. Intraocular Lenses

Intraocular lenses consist of an optic where the refractive power of the implant is concentrated, projections from this termed haptics which provide stability when implanted in the eye (*Figure 1.6*).

Figure 1.6: *Diagram of IOL*

The majority of IOL implants in routine cataract surgery are monofocal and spherical, providing clear vision at only one focal length. Emmetropia is usually the aim for distance vision with monofocal IOLs, leaving the patient with no true accommodation, although some depth of focus is present due to the pupil aperture, optical aberrations and the patient's tolerance to blur (Wolffsohn *et al.* 2010). The desire to optimize uncorrected distance vision post-surgery has resulted in the development of aspheric, toric and light-adjustable lenses (LALs). To extend the range of eye focus, multifocal designs have been developed, together with attempts to restore more natural eye focus with 'accommodating' IOL designs. Complementing these optical advances, the transmission properties of IOLs have been altered to try to protect the retina, inserters and phacoemulsification techniques have allowed smaller corneal incisions and the edges have been moulded to reduce posterior capsular opacification (PCO). In the following sections these various designs of intraocular lenses will be described.

1.6.1. Aspheric IOLs

The positive aberration of the cornea in youth is mainly cancelled out by the negative spherical aberration of the crystalline lens. In the aging eye there is increasing positive aberration which contributes to a decrease in visual quality due to imbalance of the aberration between the two structures (He *et al.,* 2003). Removal of the natural lens and introduction of a spherical IOL leaves positive aberration of the cornea creating high-order aberrations (Barbero *et al.,* 2003).

The development of aspheric IOLs has aimed to balance the spherical aberration of the cornea by introducing negative spherical aberration (Holladay *et al.,* 2002). It was estimated that aspheric lenses would decrease high-order aberrations to a level below that of the cornea in 45-86% of implantations (Wang and Koch*.,* 2005) thereby improving contrast sensitivity and visual acuity of the eye (Fahle, 2009). Aspheric lenses may be designed to be aberration-free or simply reduce levels of existing aberration; termed aberration-correcting IOLs (Buckhurst *et al.,* 2010). The performance of aspheric IOLs in comparison to spherical IOLs have shown to be superior or at least equal for distance visual acuity (Mester *et al.,* 2003; Bellucci *et al.,* 2005) and mesopic contrast sensitivity (Mester *et al.,* 2003; Packer *et al.,* 2002), although the depth of clear focus has been found to be reduced in some (Marcos *et al.,* 2005; Rocha *et al.,* 2007; Nanavaty *et al.,* 2009), but not all studies (Shentu *et al.,* 2008). However, it should be noted that the optical benefits of these IOLs are heavily reliant on their centration within the capsular bag and pupil size

(Montés-Micó *et al.,* 2009), for example decentration exceeding 0.5mm would provide no beneficial asphericity (Atchison, 1991).

1.7. Presbyopia & IOLs

Although the power of implanted conventional monofocal IOLs is usually calculated from ocular biometry to correct distance refractive error, the range of clear focus varies greatly between individuals. This range of clear focus is due to residual myopia, myopic astigmatism, monovision, corneal multifocality through aberrations and pupil miosis (Nakazawa and Ohtsuki, 1983; 1984; Nanavaty *et al.,* 2006). A combination of these factors in eyes implanted with monofocal IOLs can produce a pseudo-accommodative range of 0.7 - 5.1D (Menapace *et al.,* 2007).

Monovision, where one implant is optimized for distance vision and the other focused at a closer distance, is often targeted by surgeons to optimize the range of clear vision. The technique relies on the suppression of the blurred image from one eye by the brain, but is not tolerated by an estimated 10-20% of patients (Greenbaum, 2002; Handa *et al*., 2004). Monovision also results in stereopsis and contrast sensitivity loss, with the reduction growing with the power difference between the two eyes (Durrie; 2006). However, a recent study of IOL monovision with on average 1.2D anisometropia between the eyes has suggested that contrast and stereopsis can be maintained, although only one quarter of patients were spectacle independent (Finkelman *et al*., 2009).

To meet demands of clearer near vision and spectacle independence premium intraocular lenses have been devised to optimise vision for both distance and near. Toric IOLs aim to correct higher degrees of astigmatism for distance vision, while multifocal and accommodating designs aim to provide clarity for near tasks in addition to distance vision. The remainder of the current chapter will discuss the current premium IOL options available for implantation during cataract surgery and refractive lens exchange.

1.8. Premium IOLs

1.8.1. Multifocal IOLs

Simultaneous vision is used in IOLs to provide multifocal clear distances. Until recently, the optical designs have been concentric refractive or diffractive designs, or a combination of both. Publications on their performance have been limited by the use of non-linear Snellen acuity measurements at distance and reporting the number of people who can read Jaegar text of a certain size at near (e.g. Steinert *et al.,* 1999; Pineda-Fernandez *et al.,* 2004; Javitt and Steinert, 2000) when it is well established that Jaegar print sizes differ between charts (Mehr and Fried, 1976).

Enlargement of pupil size such as in dim conditions, exposes more annular zones of the IOL, changing the distribution of light energy between the distance and near focus of refractive IOLs, depending on the optical design. Hence refractive IOLs are dependent on pupil size and this is important to consider prior to implantation. The brain selects the in focused image and suppresses other. Such interference can lead to development of various photopic phenomena.

Although multifocal IOLs split the light entering the pupil between distance and nearer distances, most studies show comparable distance vision between multifocal and monofocal IOLs (Steinert *et al.,* 1999; Vaquero-Ruano *et al.,* 1998; Orme *et al.,* 2002) as well as improvements in near acuity and depth of focus in multifocal IOLs (Javitt and Steinert, 2000).

Refractive multifocal designs (*Figure 1.8*) comprise of concentric areas of differing refractive power usually on the anterior optic surface, created by differences in curvature for distance and near power correction. Refraction is described as the change in direction of light rays travelling from one medium to another of differing density due to a change in speed. Using this principle a refractive IOL is able to change the way in which light focuses on the retina. The changes in power within regions of a refractive IOL enable foci from a range of distances to fall on the retina simultaneously. Distance correction tends to be central with peripheral regions designated to near correction. Such lenses are distanced-biased for small pupils, allowing nearly all light energy to be used for distance viewing as peripheral near focus zones are obstructed by the pupil. Enlargement of pupil size such as in dim conditions, exposes more annular zones of the IOL, where some light energy is transferred to near focus regions and less to that of distance. When viewing in the distance regions providing distance focus form an image on the retina whilst other regions form a blurry image. These are superimposed; the brain selects the in focused image and suppresses other. Such interference can lead to development of various photopic phenomena. Most refractive IOLs are dependent on pupil size and thus this is important to consider prior to implantation.

Diffractive IOLs (*Figure 1.7*) use the Huygens-Fresnel principle of concentric eschelets on the surface of the IOL to create a diffraction pattern by acting as a grating. Unlike refractive optics, all rings work together to produce constructive and destructive interference for distance and near foci, and hence the optics are largely pupil independent. Not all the available incident light can be used by a diffractive IOL, approximately 40% of light is used for both distance and near viewing, hence contrast is lost as well as halos created by the concentric prism elements.

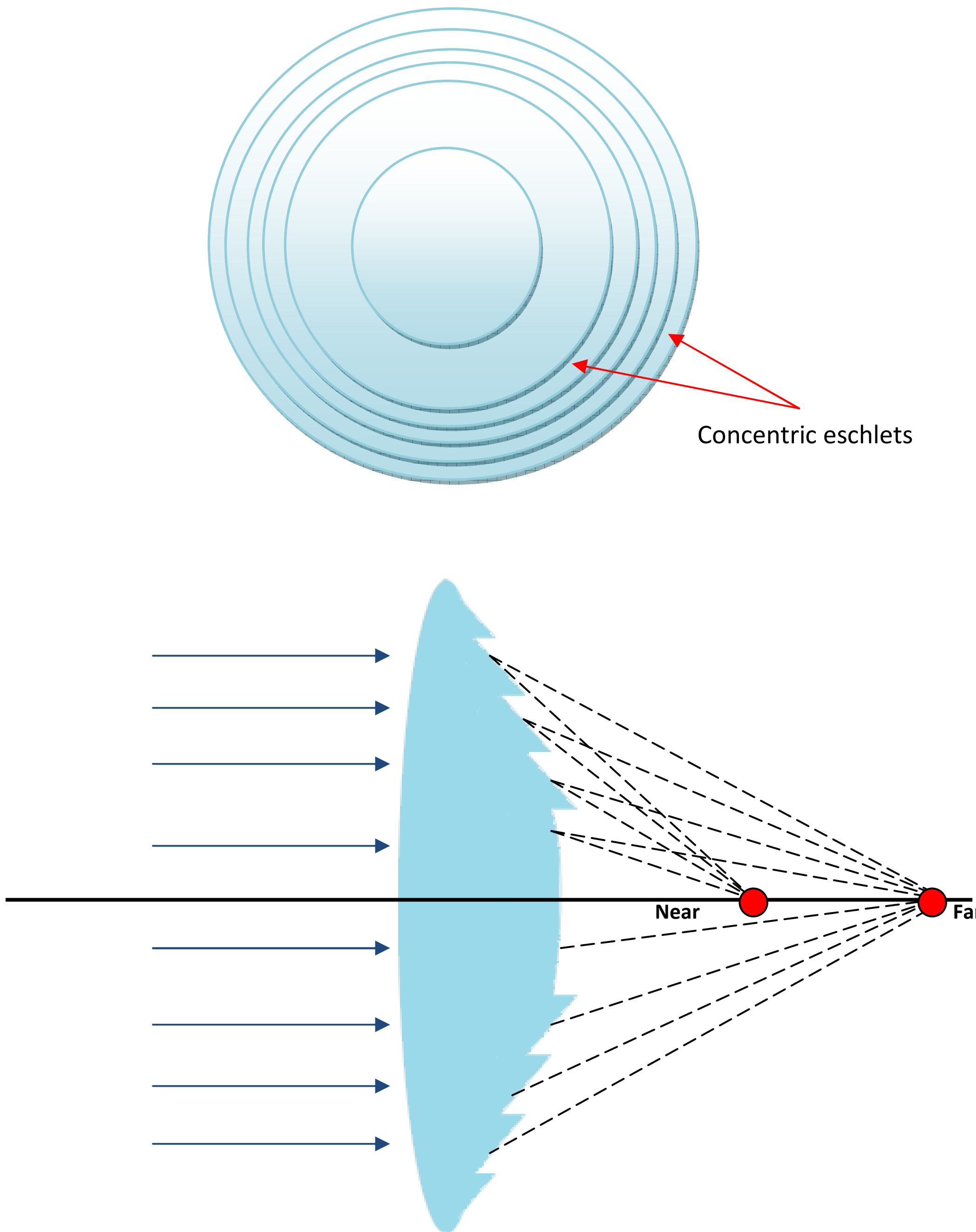
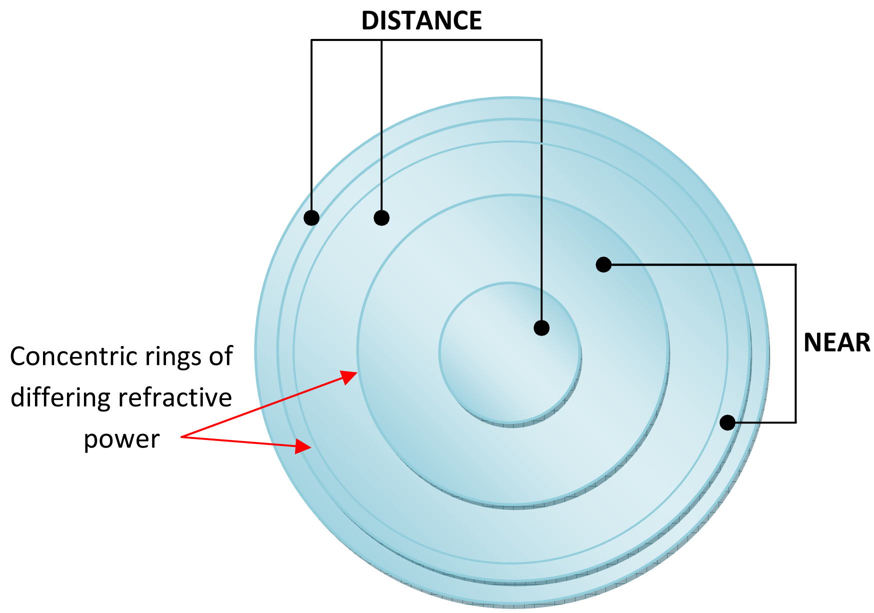


Figure 1.7: *Fully diffractive multifocal optic. Light rays diffracted to different foci through diffractive surface*



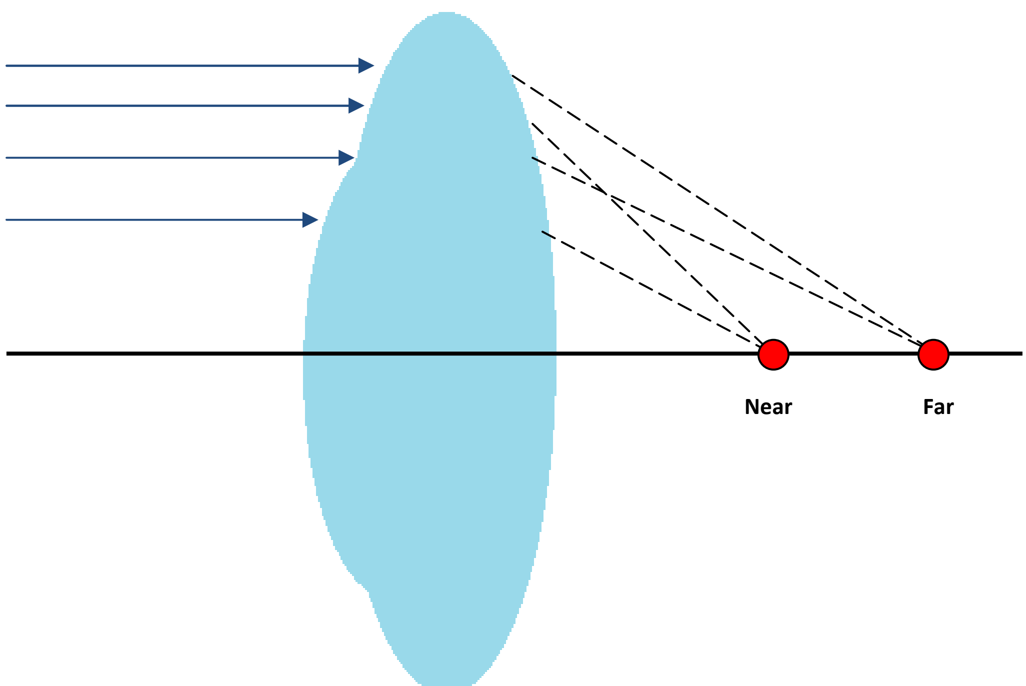


Figure 1.8: *Refractive multifocal optic. Juxtaposition of zones of differing power produces different foci.*

The third multifocal design known as apodized diffraction or 'partially diffractive' is a combination of refractive and diffractive techniques to obtain multifocality (Kohnen and Derhartunian, 2007). To achieve this, the step height at each diffraction step is gradually decreased resulting in reduced reflection at edges. The aim of such a design is to improve image quality, to reduce contrast sensitivity loss and to be less pupil dependant. Patients report high levels of spectacle independence following implantation of multifocal IOLs (e.g. Alfonso *et al.,* 2008) which indicates the benefit of their use. Distance visual acuity is often better with a distance dominant IOL, while near visual acuity shows more improvement with a near dominant lens (Steinert, 2000; Alfonso *et al.,* 2008; Kershner, 2003; Jacobi *et al.,* 2002; Choi *et al.,* 2008; Simpson, 1992; Berdeaux *et al.,* 2008). Bilateral multifocal IOL implantation generally gives better visual function (Steinert, 2000; Pineda-Fernandez *et al.,* 2004), however unilateral implantation of a multifocal IOL in those with unilateral cataracts may still prove beneficial due to possibilities of aniseikonia and anisometropia with spectacle correction (Jacobi *et al*., 1999). Mixing and matching different multifocal IOLs in the two eyes of an individual patient is now becoming a common technique to overcome the limitations of a single design (Gunenc and Celik, 2008; Goes, 2008; Hutz *et al.,* 2010).

The most recent development in premium lenses aiming to overcome presbyopia following cataract surgery is the trifocal IOL. The aim of this design is to provide better intermediate vision in addition to good distance and near vision by incorporating three foci into the optic of the IOL. Being of relatively new concept very few studies have reported the visual performance of these lenses. Although distance and near vision is maintained with the added benefit of intermediate vision there is skepticism of contrast sensitivity and dysphotopsia as this IOL is in effect of diffractive design. To date, only two studies by Voskresenkaya *et al* (2010) and Gatinel *et al* (2011) have investigated trifocal performance, the latter only being of optical bench tests. Both studies show promising results however further investigations are required within patients to fully explore the benefits of such a design.

Despite improved near visual acuity and comparable distance visual acuity to spherical IOLs, implantation of multifocal IOLs are associated with photopic phenomena such as haloes, disability glare and reduced contrast sensitivity particularly in mesopic conditions (Steinert, 2000; Richter-Mueksch *et al.,* 2002; Awwad *et al.,* 2008). Glare and halo phenomena tends to occur more in refractive multifocal IOL designs than diffractive, though contrast sensitivity shows greater impairment with diffractive designs (Pieh *et al.,* 1998; Hayashi *et al.,* 2009). However, such visual phenomenon is shown to reduce over time as adaptation occurs (Vaquero-Ruano *et al.,* 1998). The contrast sensitivity can be improved and the range of clear focus extended into the intermediate range by adding asphericity to the multifocal IOL (Alfonso *et al.,* 2008).

It is important to establish the visual demands of the patient in order to provide the most suitable near additional power. Lower adds provide better intermediate, but poorer near vision than higher additions, along with less unwanted visual effects such as reduced contrast sensitivity loss (Hayashi *et al.,* 2009). The IOL power is traditionally stated for the spectacle plane so this must be converted to the optical plane to determine the optimum working distance with the IOL implanted. Residual astigmatism after IOL implantation reduced the effectiveness of multifocal IOLs; therefore corneal astigmatism must be quantified prior to surgery and reduced by corneal relaxing incisions or a toric multifocal IOL if greater than about 1 dioptre (Hayashi *et al.,* 2010).

1.8.2. Accommodating IOLs

Current ‘accommodating’ IOLs rely on the Helmholtz theory of accommodation, where inwards and forward contraction of the ciliary muscle loosens the zonules coupling the muscle with the crystalline lens. The elastic lens capsule can then take up a more convex shape, increasing its optical power. Studies using ultrasound biomicroscopy (Bacskulin *et al.,* 1996; Stachs *et al.,* 2002) and magnetic resonance imaging (MRI) (Strenk *et al.,* 1999; 2006) demonstrating that the human ciliary muscle maintains its contractility throughout life, allows a mechanism to control an IOL through natural eye focusing structural changes. Accommodating IOLs were initially conceptualised in the 1980s by J. S. Cumming who observed remarkable near vision acuity in patients implanted with plate haptic silicone IOLs. Though pseudoaccommodation, which is described as the subjective range of clear focus enhanced by ocular aberrations, pupil size and an individual’s tolerance to blur, could not be solely responsible, measurements with A-scan ultrasonography showed movement of the IOL (Doane, 2004).

Accommodating IOLs are categorised in accordance to their mechanism of action (Sheppard *et al.,* 2010). Assessment of the performance of accommodating IOLs must separate true accommodation from pseudoaccommodation. Many studies have attempted to image the lens mechanism using pharmacological (2% pilocarpine) rather than physiological methods to stimulate the ciliary muscle, but the resulting change shows the maximum potential of the implant rather than the natural or achievable objective accommodation (Koeppl *et al.,* 2005). The following will discuss the various types of accommodating IOL designs.

1.8.2.1. Single-Optic IOLs

Single optic IOLs (*Figure 1.9*) were designed to move forward with contraction of the ciliary muscle, either due to the forward movement of the capsule and contraction of the lens equator pushing against a hinge mechanism, or due to the increased vitreous pressure from the ciliary muscle bulk displacement into the vitreous chamber (Glasser, 2008). The space in the anterior chamber limits the potential objective accommodation of single optic-shift IOLs to approximately 1.5D (for a maximum 1mm movement; McLeod *et al.,* 2003). Although dynamic objective accommodation has been shown (Wolffsohn *et al*., 2006a), the average objective accommodation is only as much as 0.75D (Wolffsohn *et al.,* 2006b; Menapace *et al*., 2007) and decreases with increased time after surgery. One study investigating the performance of the 1CU accommodating lens (HumanOptics AG, Erlangen, Germany) reported a decrease in objective accommodation of -0.19 ± 0.44D with a corresponding decrease in subjective measurement of -0.25± 0.59D two years following implantation (Wolffsohn *et al.*, 2006a,b). More recently it has been shown that the mechanism of action mainly to be due to the flexing of the lens changing the high order aberrations, although not in a systematic manner between individuals (Wolffsohn *et al.,* 2010). PCO rates are also high due to the IOLs not forming a restrictive kink in the capsule with lens fibrosis following cataract surgery (Sheppard *et al.,* 2010).

Figure 1.9: *Single-Optic accommodating IOL mechanism*

1.8.2.2. Dual-Optic IOLs

Dual-optic IOLs consist of a biconvex anterior optic with a power of approximately 32D and a posterior negatively powered haptic which is altered in power to correct for the patients ocular biometry. The optics are separated by connecting spring haptics, which are designed to push the optics further apart on contraction of the ciliary muscle to create an inwards equatorial tension from the crystalline lens capsule. The optics therefore take the form of a Galilean telescope and can deliver up to 4.0D of power change within the confines of the anterior chamber (McLeod *et al.,* 2007). Currently, there is only one published report on the clinical performance of such an IOL. The Synchrony dual-optic accommodating IOL (Visiogen, Irvine, CA) (*Figure 1.10*) was reported to give 3.2 ± 0.9D of accommodation (Ossma *et al.,* 2007), although the defocus curve presented has no error bars and is symmetrical around zero dioptres which casts doubt over the methodology used. However, the low PCO rate reported supports the view that holding the lens capsule open after cataract surgery may limit epithelial cell migration to the posterior pole.

Aston University

Illustration removed for copyright restrictions

Figure 1.10: *Synchrony dual-optic accommodating IOL*

1.8.2.3. Curvature Change IOLs

The natural change in optical power with the relaxation of the lens zonules occurs principally due to the crystalline lens curvature increasing rather than the lens moving forward in the eye (Davies *et al.,* 2010). Hence, ideally accommodating IOLs would work by a similar mechanism, resulting in much larger changes in optical power being possible. No commercially available IOLs using this mechanism are currently available although some are described in the literature. The most natural restoration of accommodation would be from lens refilling once the cataract has been removed. The capsulorhexsis would have to be small, peripheral and able to be effectively sealed. Although much research has been conducted into achieving this procedure, sealing the capsular bag and preventing the proliferation of epithelial cells to the posterior pole of that capsule, where the traditional treatment with YAG laser would destroy the accommodating lens, have resulted in a lack of progress to clinical trials (Nishi *et al.,* 2009).

The FluidVision IOL (PowerVision Inc, Belmont, CA) has fluid channels connecting a hollow haptic to the optic that can retain fluid. On contraction of the ciliary muscle, fluid from the haptics is pushed into the optic increasing its volume and equatorial diameter and hence causing an increase in power, with a potential of 8D change in lens curvature (Pepose, 2009). A recent paper described the NuLens (NuLens Ltd.) (*Figure 1.11*) which uses the capsular bag as a diaphragm, whose forward movement from the contraction of the ciliary muscle bulges a transparent silicone gel through an aperture causing a curvature change. Despite suggesting a large change in optical power of the IOL is possible from the 0.1-0.2mm movement of the gel lens sag, the current design reduces the optical power on accommodation (Alio *et al.,* 2009).

Aston University

Illustration removed for copyright restrictions

Figure 1.11: *NuLens accommodating IOL*

1.8.3. Toric IOLs

Approximately 20% of patients requiring cataract surgery present with over 1.50 dioptres of corneal astigmatism (Hoffer, 1980; Ferrer-Blasco *et al.,* 2009). The effect of which has not been determined on daily life. While any residual astigmatism can be corrected with spectacles, refined biometric techniques enable the selected IOL power to leave little residual spherical refractive error. With more patients desiring to be spectacle independent for distance viewing, more efforts to minimize residual astigmatism during cataract surgery must be made to meet such demands (Buckhurst *et al.,* 2010).

Skilled surgeons can use corneal (CRIs) or limbal relaxing incisions (LRIs) to reduce post-operative astigmatism. These involve partial thickness incisions along the axes of the astigmatism with the depth and arc length relating to the degree of pre-operative corneal astigmatism. However, wound healing variability limits the accuracy and magnitude of the effect (Amesbury and Miller, 2009). The toric IOL (*Figure 1.12*) was so forth devised in the mid 1990's to eliminate the need for incisional surgery and increase spectacle independence for astigmats (Medicute, 2008).

Aston University

Illustration removed for copyright restrictions

Figure 1.12: *Toric IOL*

Implantation of a toric IOL requires careful determination of corneal cylindrical power. Manual or automated methods can be used, with newer biometry devices measuring axial length and corneal curvature (Buckhurst *et al.,* 2009). Ideally corneal topography should be confirmed by a second device (Budak *et al.,* 1999) and the operator should be well trained (Cronje *et al.,* 1999). Prior to surgery, reference marks are placed at the limbus for the alignment of the IOL. The patient must be upright for application of these exterior markings due to deviation of the eyes in a supine position (Horn, 2007) which may lead to misalignment of the IOL. Newer techniques involve digital imaging of the eye to allow alignment of the toric IOL axis to predetermined iris features or bulbar conjunctival features (Wolffsohn and Buckhurst, 2010) and in the future the chosen axis will be presented through the surgical microscope, tracked to the orientation of the orbit. Studies have presented visual improvements with toric IOLs, though post-operative rotation of toric IOLs is still a concern (Gills *et al.,* 2002; Sun *et al.,* 2000; Buckhurst *et al.,* 2010). Deviations from the correct axis will reduce the effective power of the cylinder, with a rotation of 30º or more providing no cylindrical correction (Shimzu *et al.,* 1994).

Rotation after IOL implantation occurs mainly due to compression of the haptics caused by contraction of the capsule through fibrosis. Friction between the haptics and the capsule are important for reducing IOL rotation, as is the haptic design and careful removal of the viscoelastic from around the IOL after lens implantation (Buckhurst *et al.,* 2010). Stabilization does occur within a few days to weeks, probably due to joining of the anterior and posterior capsules holding the IOL in a fixed position (Shimzu *et al.,* 1994; Buckhurst *et al.,* 2010). Rotation is reported as less with open loop haptics than plate haptics, although plate haptics show better long-term stability (Parssinen *et al.,* 1998). Newly introduced closed-loop haptics may be more stable during capsular compression though this requires further research (Buckhurst *et al.,* 2010).

Repositioning a rotated lens is possible, although it is more complicated and difficult to achieve the longer after the original surgery it is attempted due to fibrosis with the lens capsule. Lens extraction and repositioning is considered optimum approximately 1 week after surgery as earlier may allow the lens to re-rotate and later than two weeks following implantation will cause difficulty in trying to reposition due to fusion of the capsule (Novis, 2000). It has associated risks such as cystoid macular oedema, capsular tears and endophthalmitis and thus is favourable to avoid (Sun *et al.,* 2000).

1.8.4. Blue-Light Filtering IOLs

The visual spectrum spans from 400 to 700nm. It is widely known and accepted that exposure to UV radiation and blue light is harmful to retinal structures (Mainster *et al.,* 1983). In order to protect the eye the cornea absorbs wavelength below 295nm, the remaining wavelengths 300-400nm are then blocked by the crystalline lens. Despite this some blue light still reaches the retina and crystalline lens removal through cataract surgery will leave the retina further exposed if the IOL transmits harmful wavelengths.

It has long been known that blue light is associated with an increased risk of development of macular degeneration (Mainster *et al.,* 1983). The blue light causes the production of reactive oxygen species (ROS), being extremely reactive, these cause damage mainly to the retinal pigment epithelium (RPE) (Ham *et al.,* 1980; Boulton *et al.,* 2001). Lipofuscin within the RPE absorbs short wavelengths due to its component A2E (light absorbing chromophore), that has a peak absorbance of 335-435nm (Sparrow *et al*., 2000). Absorption results in production of ROS leading to RPE apoptosis and eventually cellular death. It is suggested that the levels of A2E increase with age. Natural cellular defenses against ROS production include; superoxide dismutase, catalase, phospholipase and pigments such as xanthophylls (Patel, 2007). Macular pigment can only be obtained from diet and possesses antioxidant properties; it absorbs blue light providing protection for the retina. Also, with age, oxidative changes occur in the crystalline lens causing ‘brunescence’ or yellowing of the lens, due to an accumulation of chromophores (Brockmann *et al.,* 2008). Thus its absorbance widens to 400-500nm providing further protection against shorter wavelengths of light. The young lens also contains a short wavelength filtering substance 3-Hydroxykynurenine-glucoside, however the ageing yellowing lens provide three times more protection (Benz *et al.,* 2007).

It may therefore be argued that on cataract extraction, replacement with a clear IOL removes natural protection and increases the risk of macular degeneration and retinal phototoxicity as transmission of shorter wavelengths of light (UV and blue) will be increased (Brockmann *et al.,* 2008). Originally IOLs were constructed from PMMA with no form of UV filtration allowing all UV through to the retina. In 1978 it was identified that UV radiation (100-400µm) was harmful to the retina (Mainster, 1978). Some IOLs have shown to transmit more than 10% of wavelengths 350-400nm which is not adequate protection against UVA (Laube *et al.,* 2004). By the 1980’s chromophores were incorporated into most IOLs to block UV light. However these IOLs still transmit an undesirable amount of blue light (Henderson *et al.,* 2010) thus the RPE is still vulnerable to damage. This has driven the development of blue light filtering IOLs (*Figure 1.13*). Chromophores are added to the IOL which block blue light; the IOL takes on a yellow appearance and hence are also known as ‘yellow’ IOLs.

Aston University

Illustration removed for copyright restrictions

Figure 1.13: *Blue-filtering IOLs*

Despite the proposed benefits of yellow IOLs there has been much debate over light filtering and its significance to ocular health (Henderson *et al.,* 2010). There has been speculation over the effects on contrast sensitivity, colour perception, glare sensitivity, scotopic vision and circadian cycle. In general no clinical effects have been measured (Hayashi and Hayashi, 2006; Brockmann *et al.,* 2008), although some investigators have found a reduction in scotopic sensitivity which could increase the risk of falls in the elderly (Schwiegerling, 2006). More recently, concern with blocking blue light from reaching the retina has focused on sleep regulation through the circadian rhythm. A substance called melanopsin within the retinal ganglion cells is stimulated by blue light which aids the control of melatonin, via the pineal gland which is associated with sleep regulation. In dark conditions less blue light is available to stimulate melanopsin therefore the pineal gland secretes melatonin which causes sleeping. With bright light the secretion is reduced causing an increase in attention. Thus reduced transmission of blue light due to yellow IOLs may cause deregulated sleeping patterns (Mainster, 2006). An estimated 27-38% decrease in melatonin suppression is reported by Mainster (2006). However, this is in comparison to a UV filtering IOL and not an opacified cataractous lens where all light transmission is significantly reduced (Henderson *et al.,* 2010). Hence Edwards and Gibson (2010) in their recent review conclude "*The real value of blue-blocking lenses in preventing AMD or its progression has yet to be shown and, while there would not appear to be any proven significant limitations associated with these lenses, the current trend of using evidence based* *medicine to determine treatment modalities would seem to be missing for these lenses which attract a price premium".*

1.8.5. Light Adjustable Lens (LALs)

As IOLs are implanted in the eye, patients cannot test the effects as easily as they can with spectacles and contact lenses. Even after accurate biometry, wound healing can lead to unexpected residual refractive error. To overcome this and allow post-implantation adjustment of the IOL power and multifocality, a Light Adjustable Lens implant (LAL) has been introduced (Calhoun Vision, Inc, Pasandena, California). The lens implant consists of light-sensitive macromers in an X-linked silicone matrix that are sensitive to ultraviolet light (365nm). Exposure of UV light controlled and monitored by a digital computer system, induces polymerisation of the macromers to create an interpenetrating polymer in the lens, causing thickening in that area (von Mohrenfels, *et al.,* 2010). The non radiated macromers diffuse into areas free of UV radiation exposure and this leads to changes to the shape and or refractive index of the LAL (*Figure 1.14*). Myopic changes are achieved by applying UV emission on the periphery of the LAL, effectively thickening that zone. A hyperopic change is thus achieved by directing the beam towards the centre of the LAL. This adjustment is current performed two weeks post-operatively usually followed by two lock-in exposures. Each session allows a change of up to 2D. To correct presbyopia, monovision can be tested in-vivo to see how the patient adapts and the lens profile can also be made multifocal

(Hengerer *et al.,* 2009). If the patient cannot tolerate their correction, it can be adjusted or removed.

Aston University

Illustration removed for copyright restrictions

Figure 1.14: *Mechanism of adjusting power of LAL*

1.8.6. Phakic IOLs

IOLs that can be implanted in the anterior chamber have been developed to correct refractive error without affecting natural accommodation in pre-presbyopes (Figure 1.15). These lenses are generally used in patients whose refractive error is too high to correct by laser refractive surgery and where the corneal thickness was not adequate to allow the ablation depth required to correct their ametropia. Endothelial loss leading to a loss in corneal transparency and cataract still remain the two main concerns with such implantation, despite the effectivity, predictability and general safety having improved (Espandar *et al.,* 2009).

Aston University

Illustration removed for copyright restrictions

Figure 1.15: *Phakic IOL*

1.9. Conclusion

While many advances have been made in IOL designs, the benefits of premium IOLs have not been well established, nor when they should be considered as an optical correction. Implanting advanced optical designs also raises more complex surgical issues relating to IOL rotation and centration which deserve attention to optimise the visual results. This thesis therefore examines the benefits of astigmatic correction with a toric lens over the mean spherical equivalent and how pupil dilation influences the alignment of these lenses. Centration of IOLs during surgery and over the following 6 months will also be examined.

There is a clear requirement for correction of presbyopia. Reports of global prevalence of functional presbyopia in 2005 estimated 1.04 billion cases, which is expected to escalate to 1.4 billion in 2020 and 1.6 billion in 2050 (Holden *et al.,* 2008). While many non-surgical options for presbyopia exist, such as spectacles and contact lenses, there is some interest in presbyopic IOLs, which are usually fitted when cataracts have developed, to implant them when presbyopia first occurs. This would allow spectacle independence in addition to removing the probable need for cataract surgery later in life when other age related health problems may make surgery more complex and risky. Hence, better methods to measure residual accommodation will be explored along with what factors, other than age, affect when an individual becomes presbyopic and therefore should consider elective IOL surgery with implantation of a premium IOL. Finally, the benefits of a new type of IOL, a trifocal diffractive design, is evaluated to determine the range of clear vision offered as well as the visual compromises experienced.

CHAPTER 2

Effect of Uncorrected Astigmatism- Implications for Toric Intraocular Lenses

2.1. Introduction

Corneal astigmatism is ametropia due to irregular surface curvature of the cornea, where two perpendicular meridians give different focal powers (*Figure 2.1*). The result is two foci with a blurred area between them known as the interval of Stürm, giving rise to blurred vision (Zadnik, 1997).

Figure 2.1: *Foci with corneal astigmatism*

It is a common condition, occurring in about 85% of the general population, with 20-30% of the older population (>60 years), when cataracts are most common, having significant severity (>1 dioptre) (Vitale *et al.,* 2008; Ferrer-Blasco *et al.,* 2009). During routine cataract surgery, enhanced biometric techniques now allow the approximation of IOL power to fully correct spherical errors leaving the patient, in most cases, spectacle free for distance vision. Correction of astigmatism, however, presents more difficulty; traditionally corneal relaxing incisions (CRIs) or astigmatic keratotomy and limbal relaxing incisions (LRIs) are used in order to reduce post-operative astigmatism (Lindstrom 1990; Thornton 1990). CRI's appear more 'effective' but LRIs tend to be preferred amongst surgeons as are considered safer (Gills *et al.,* 2002). Reducing higher levels of astigmatism requires numerous incisions leading to complications such as corneal distortion. LRIs although extensively used are therefore limited to lower astigmatic errors. Predictability of incision surgery is also variable and can result in over- or under-correction, skills of the surgeon and variability amongst healing responses are also factors affecting surgical outcome (Lindstrom *et al.,* 1994; Thornton, 1994; Abbey *et al.,* 2009). The toric IOL, first devised by Shimzu *et al* in 1994 (Mendicute, 2008) aims to eliminate the need for incisional surgery and increase spectacle independence. Various studies have reported successful reduction in astigmatism with toric implants and good satisfaction rates (Ruíz-Mesa *et al.,* 2009; Dardzhikova *et al.,* 2009; Ahmed *et al.,* 2010). A study by Sun *et al* (2000) of 130 toric implantations documented 84% achieving uncorrected visual acuities of 20/40 or better. Implantation of toric

IOLs may therefore enhance a patient's perception of clarity of vision regardless if reflected in visual acuities.

While it is standard practice to correct astigmatism when prescribing glasses and about one third of prescribed contact lenses correct astigmatism (Morgan & Efron, 2009), many public health services consider intraocular lenses that correct astigmatism as specialist devices. Therefore, older astigmatic patients desiring optimum vision following their cataract operation must pay for both the intraocular lens (IOL) and the cost of private surgery. Suboptimal vision is associated with reduced quality of life and an increase in falls in the elderly (Black & Wood, 2005; Lotery *et al.,* 2007), however the impact of uncorrected astigmatism has not previously been assessed.

Since the advent of intraocular lens correction following cataract surgery in the 1950's, surgical techniques and intraocular lenses have developed rapidly to keep pace with the increasing demand created by expanding life expectancy and a corresponding more active lifestyle in patients experiencing cataracts. Therefore this study examines the challenges of uncorrected astigmatism in everyday life in people of the age when cataracts typically form to determine the need for toric intraocular lenses to be implanted as the routine standard of care.

2.2. Methods

Twenty-one presbyopes, aged 50-69 years old (58.9 ± 2.8 years, ten females) with no ocular pathology, not on medication likely to influence the stability of refractive error, having less than 0.75D of manifest astigmatism and binocular acuity better than 0.0 logMAR were recruited. Due to the nature of the glare tests involved it was important to exclude patients with epilepsy. The study conformed to the declaration of Helsinki and was approved by the institutional ethics committee. Subjects gave their informed consent to take part.

Each of the subjects were made familiar with the assessments of visual function. Visual acuity and contrast sensitivity was assessed binocularly using a Thomson computerised logMAR progression Test Chart (Thomson Software Solutions, Hatfield, UK). Subjects were asked to read the smallest visible letters and were encouraged to guess when uncertain. Each letter was scored as 0.02logMAR and the acuity measured with 95%, 50% and 10% contrast letters, randomised between measures. Near acuity and reading speed at 0.2 logMAR larger than this acuity was assessed at a 40cm working distance with a +2.50D near addition using standardised reading performance texts of 830 ± 2 characters length (Hahn *et al.,* 2006). The chart was presented on an LCD computer screen and the words were changed between each repetition. Light scatter in the right eye was assessed using the C-Quant straylight meter (Oculus Optikgerate GmbH, Wetzlar, Germany), recording the average of three repeated measured (*Figure 2.2*). Driving was simulated using a split attention task displayed on a 14” computer monitor. Subjects responded to the car in front travelling at a matched 60mph breaking (and increasing in visual angle) or a pedestrian initially seen at 3.6° eccentricity on the off or far side beginning to cross the path of the subject when they reached 6.5° eccentricity (*Figure 2.3*). Reaction times were averaged for 3 repeats of each condition over a 1.5 minute simulated drive. Finally mobile phone screen and internet computer screen clarity (*Figure 2.4*) positioned at the subject’s standard working distance for that task were each subjectively rated as a percentage, whilst viewing binocularly.

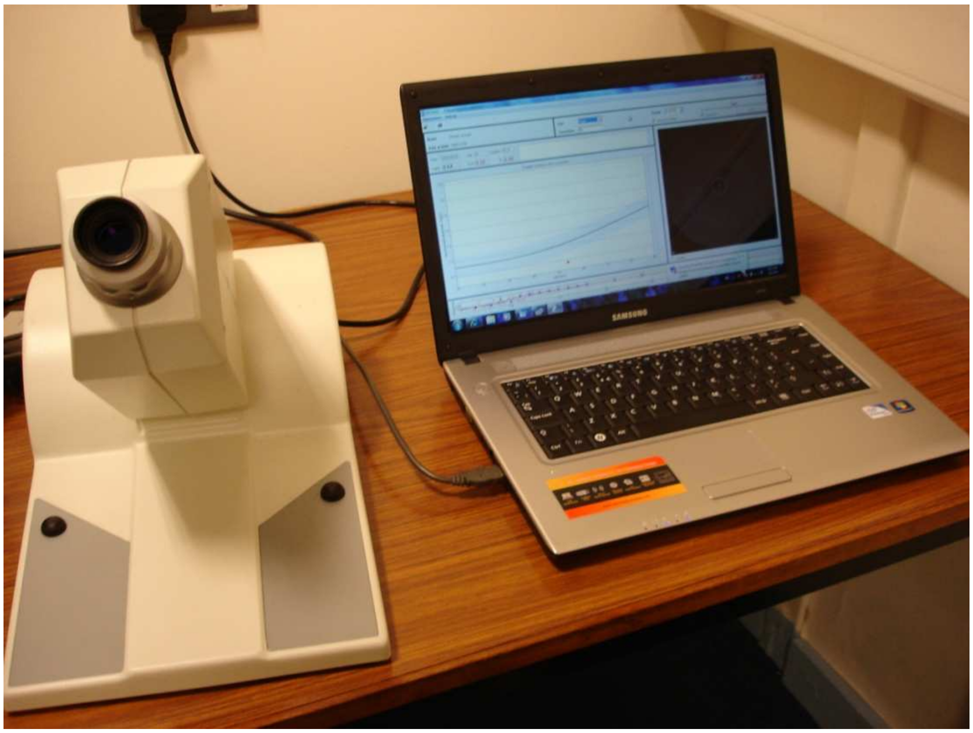


Figure 2.2: *Cquant straylight meter*

Figure 2.3: *Driving Simulator*

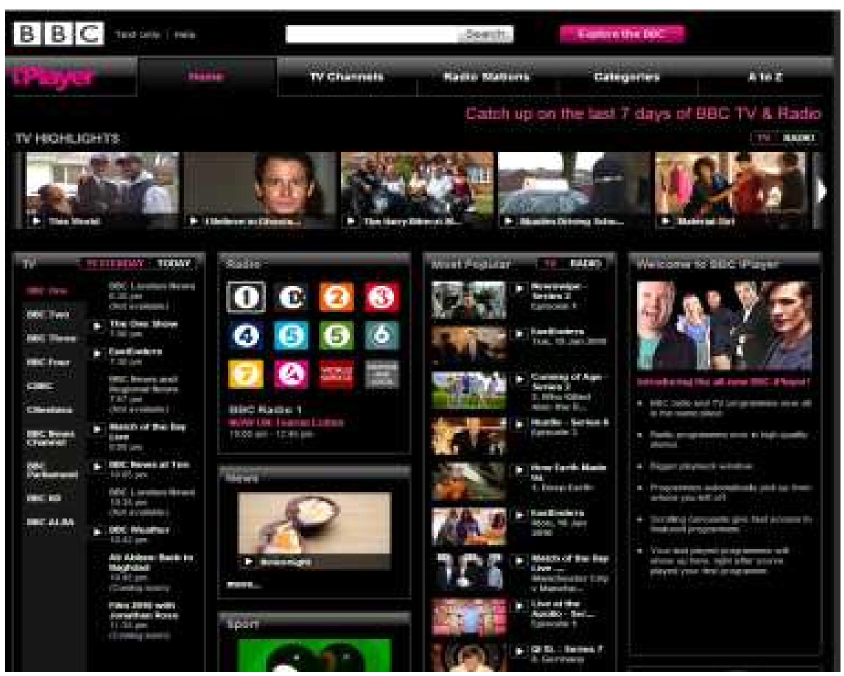


Figure 2.4: *Web page used for subjective rating of clarity*

Having practiced each of the tasks until they felt comfortable and had a consistent performance, subjects repeated the tasks seven times wearing a trial frame with spectacle lenses fitted to correct their refractive error together with a cylindrical addition of different powers and axes in randomised order compensated with a sphere so the mean spherical equivalent was always zero (*Table 2.1*). They had approximately 5 minutes to adapt to each set of lenses before testing, although it appears the brain does not adapt to binocular astigmatism (Yehezkel *et al.,* 2005).

Effect of uncorrected astigmatism:	**Full sphero-cylindrical refractive error**	**Effect of uncorrected astigmatism:**	**Full sphero-cylindrical refractive error**
	+0.00 / -0.00 x 90		+1.50 / -3.00 x 90
	+0.50 / -1.00 x 90	**AXIS**	+1.50 / -3.00 x 180
POWER	+1.00 / -2.00 x 90		+1.50 / -3.00 x 45
	+1.50 / -3.00 x 90		
	+2.00 / -4.00 x 90		

Table 2.1: *Trial lens combinations used to simulate uncorrected astigmatism*

The lens combinations simulated the typical situation of patients with an astigmatic corneal refractive error being implanted with a spherical intraocular lens of a power to compensate the average refractive error for distance, i.e. based on the average corneal curvature. To compensate for the effects of the trial lens surfaces, the minimal astigmatism comparison was simulated with the same number of trial lenses as the other conditions. The effects of uncorrected astigmatism power was assessed with the negative cylinder orientated vertically (90°) as this is the commonest cylindrical axis up to approximately 60 years of age (Ferrer-Blasco *et al.,* 2009). A three dioptre cylinder was chosen as the power at which to assess the effect of the cylinder axis as this encompasses 95% of astigmatic errors in this population (Ferrer-Blasco *et al.,* 2009).

2.3. Statistical analysis

Descriptive statistics of mean and standard deviation were plotted for each assessment. Kolmogorov-Smirnov tests were performed to check normality of data. Visual acuity, contrast sensitivity, reading speed, light scatter and reaction time data were compared using repeated measure analysis of variance with paired t-tests for post hoc testing. The linearity of changes was assessed with Pearson's correlations. Subjective ratings of clarity were compared using Fisher non-parametric related sample comparisons with Wilcoxon signed rank tests for post hoc testing.

2.4. Results

Distance visual acuity decreased significantly with increasing uncorrected astigmatic power ($F = 174.50$, $p < 0.001$) and was reduced at lower contrasts as expected ($F = 170.77$, $p < 0.001$), with no interaction between these effects ($F = 1.47$, $p = 0.26$). Each dioptre of uncorrected astigmatism caused a significantly lower acuity than the previous power at each contrast level ($p < 0.01$; *Figure 2.5*). Distance visual acuity was significantly affected by uncorrected astigmatic axis ($F = 5.19$, $p = 0.02$) and was reduced at lower contrasts as expected ($F = 129.75$, $p < 0.001$), with no interaction between these effects ($F = 0.36$, $p = 0.83$). Uncorrected astigmatism at 90° orientation resulted in a significantly better acuity than with the axis at 45° or 180° at each contrast level ($p < 0.05$; *Figure 2.5*). On average uncorrected astigmatism caused a reduction of 1.5 lines per dioptre (+0.15 ± 0.03 logMAR/DC, $r = -0.76$) in visual acuity at high contrast and a similar effect at 50% and 10% contrast (+0.14 ± 0.03 logMAR/DC, $r = -0.91$; +0.14 ± 0.05 logMAR/DC, $r = -0.80$, respectively)

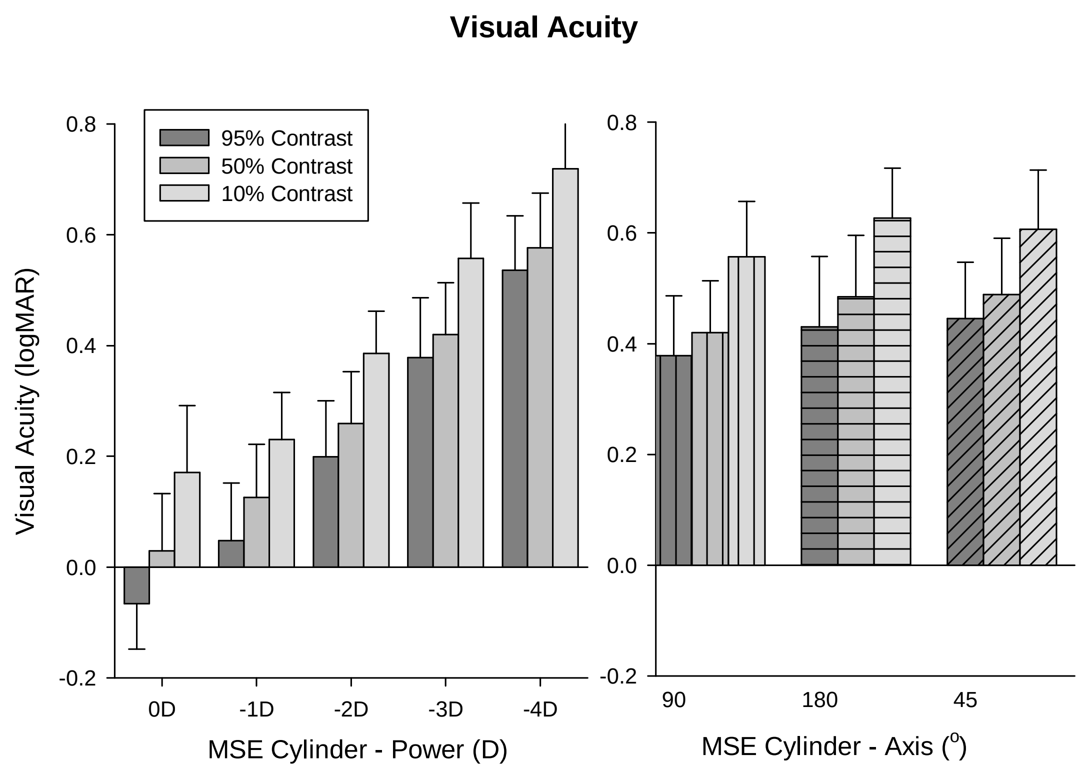


Figure 2.5: *Distance visual acuity with uncorrected astigmatism power and axis. N=21. Error bars = 1 S.D.*

Near visual acuity decreased significantly with increasing uncorrected astigmatism power ($F = 221.62$, $p < 0.001$). Each dioptre of uncorrected astigmatism caused a significantly lower acuity than the previous level ($p < 0.001$; *Figure 2.6*). Near visual acuity was significantly affected by uncorrected astigmatic axis ($F = 26.00$, $p < 0.001$). Uncorrected astigmatism at 90° orientation resulted in a significantly better acuity than with the axis at 45° or 180° at each contrast level ($p < 0.001$; *Figure 2.5*). Reading speed decreased significantly with increasing uncorrected astigmatism power ($F = 11.97$, $p < 0.001$), but only with -3.0DC or greater ($p<0.001$; *Figure 2.7*). Reading speed was significantly affected by uncorrected astigmatic axis ($F = 4.45$, $p = 0.03$). Uncorrected astigmatism at 180° orientation resulted in a significantly worse reading speed than with the axis at 45° ($p = 0.03$; *Figure 2.6*).

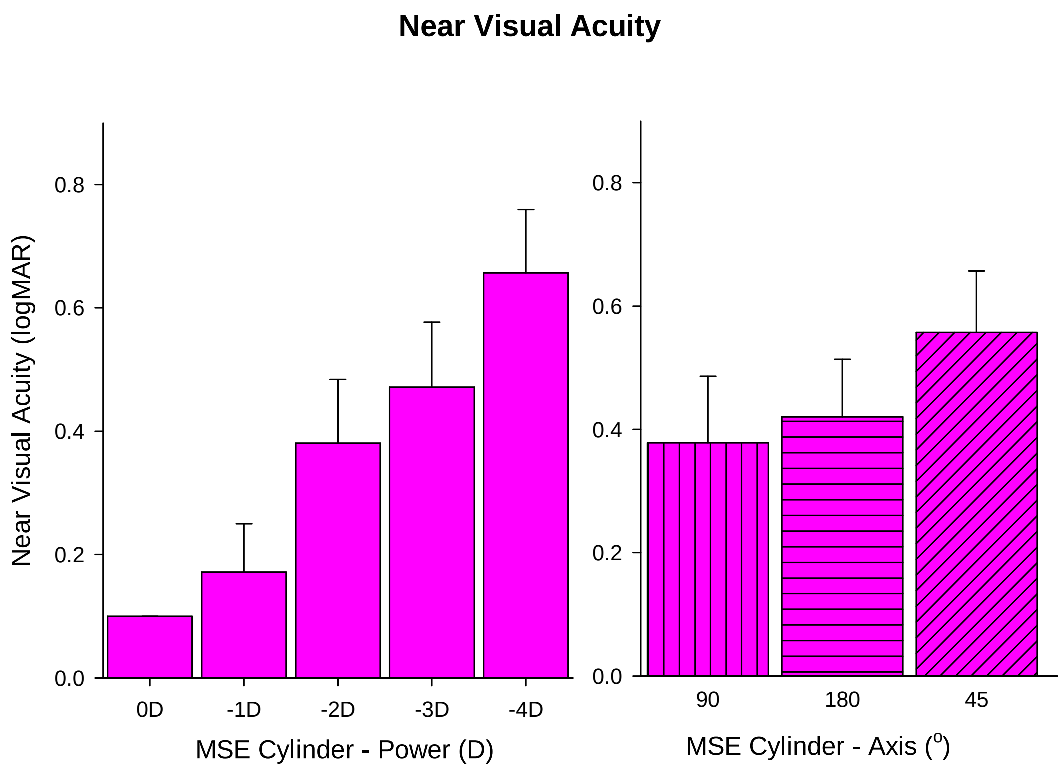


Figure 2.6: *Near visual acuity with uncorrected astigmatism power and axis. N=21. Error bars = 1 S.D.*

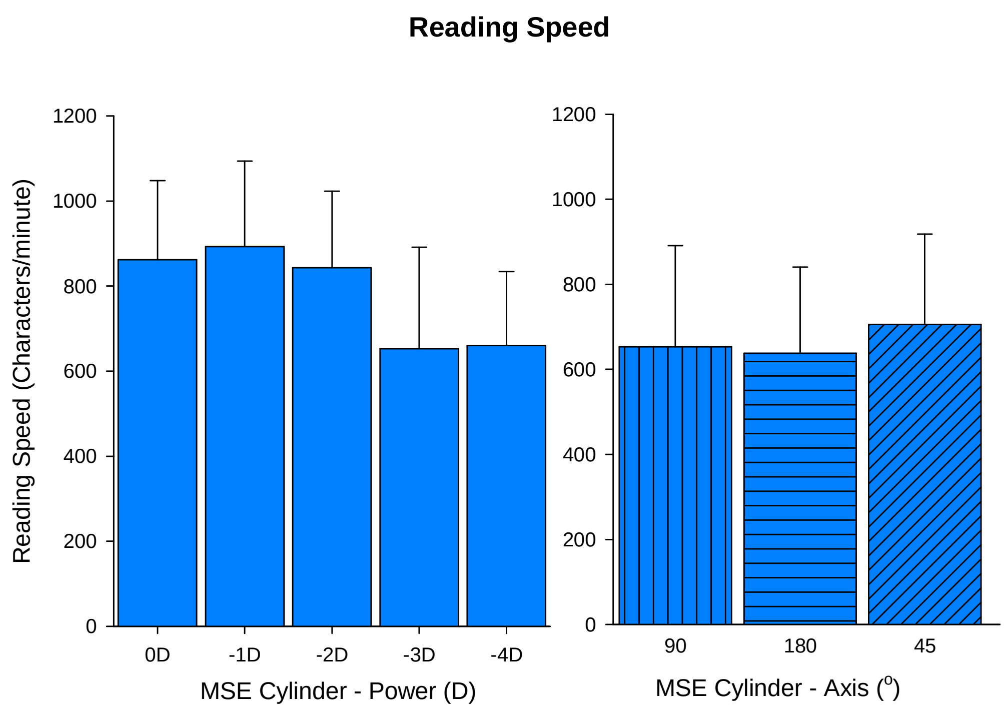


Figure 2.7: *Reading speed with uncorrected astigmatism power and axis. N=21. Error bars = 1 S.D.*

Although there was no significant increase in light scatter with increasing uncorrected astigmatism power (F = 1.11, p = 0.559) or changes in axis (F = 0.13, p = 0.878; *Figure 2.8*), the reliability and variability of measurements decreased with increasing uncorrected astigmatic power (F = 2.93, p = 0.026; F = 2.44, p = 0.05).

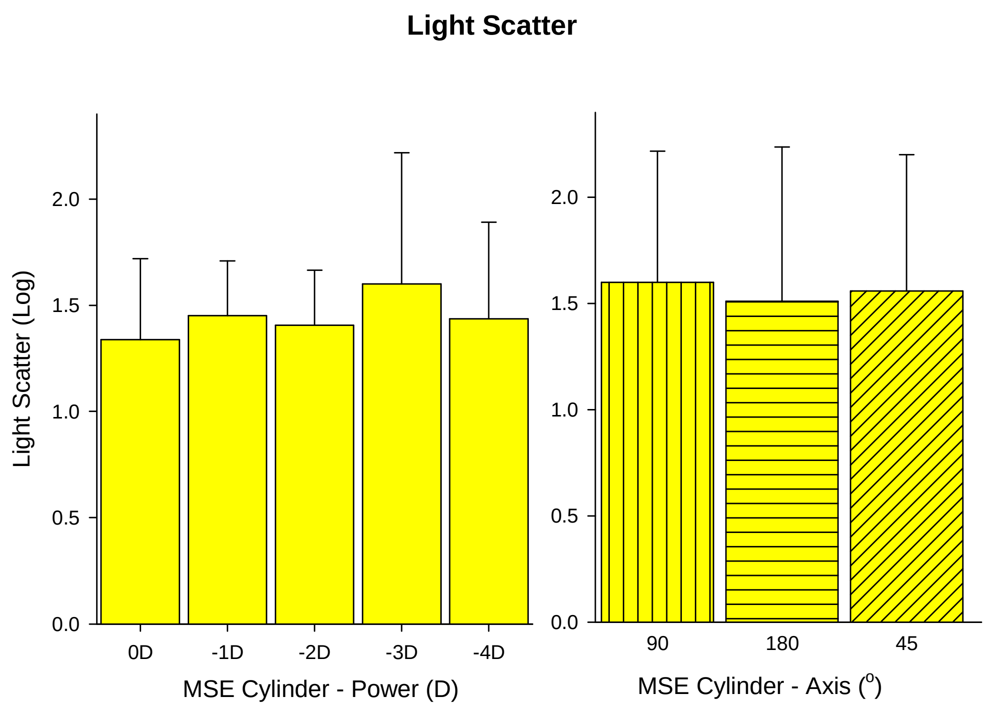


Figure 2.8: *Light scatter with uncorrected astigmatism power and axis. N=21. Error bars = 1 S.D.*

Responding to a car in front braking ($F = 0.813$, $p = 0.521$) or a nearside ($F = 1.266$, $p = 0.290$) or offside ($F = 0.200$, $p = 0.102$) pedestrian was not significantly affected by uncorrected astigmatic power (Figure 5). Responding to a car in front breaking ($F = 0.111$, $p = 0.895$) or a nearside ($F = 1.148$, $p = 0.327$) or offside ($F = 1.441$, $p = 0.249$) pedestrian was unaffected by uncorrected astigmatic axis (*Figure 2.9*).

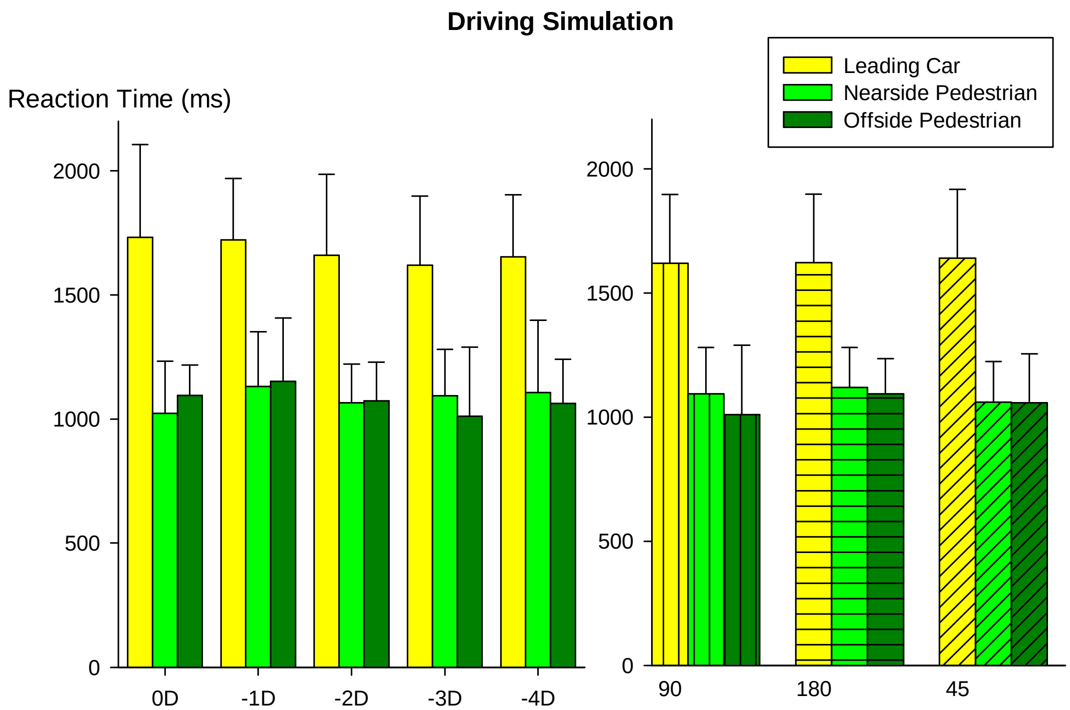


Figure 2.9: *Driving task performance with uncorrected astigmatism power and axis. N=21. Error bars= 1 S.D.*

Subjective rating of clarity decreased significantly with increasing uncorrected astigmatic power when viewing a mobile phone (Chi Squared = 81.29, $p < 0.001$) or a computer screen (Chi-Squared = 79.91, $p < 0.001$). Each dioptre of uncorrected astigmatism caused a significantly lower rating of clarity ($p < 0.01$; Figure 6). Subjective clarity was significantly affected by uncorrected astigmatic axis when viewing a mobile phone (Chi-Squared F = 19.01, $p < 0.001$) or a computer screen (Chi-Squared = 21.53, $p < 0.001$). Uncorrected astigmatism at 90° orientation resulted in a significantly better rating than with the axis at 180°, and the 180° orientation was rated significantly better than the 45° orientation for both mobile phone and computer viewing ($p < 0.01$; *Figure 2.10*).

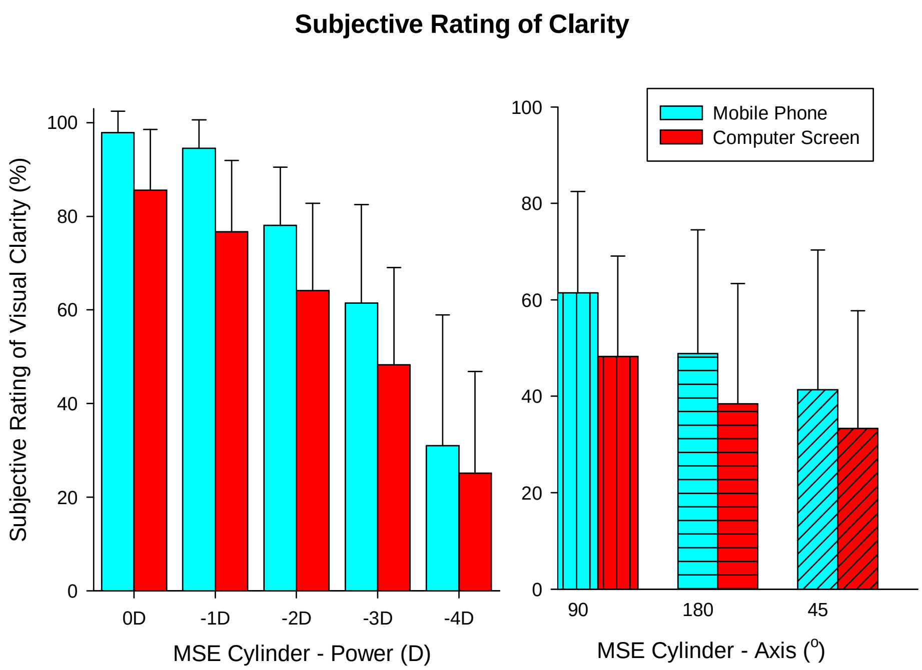


Figure 2.10: *Subjective rating of clarity with uncorrected astigmatism power and axis. N=21. Error bars= 1 S.D.*

2.5. Discussion

The present study assessed whether leaving patients with uncorrected astigmatism after cataract surgery and implantation of an intraocular lens has a significant impact on their visual function and visual performance. Visual acuity at high and low contrast sensitivity is critical to performing tasks as diverse as reading road signs and navigating. After cataract surgery, few patients report difficulties with vision for driving in daylight (5%), but almost half (43%) find night driving difficult due to glare associated with low contrast visual acuity (Monestam *et al.,* 2006). The driving standard is usually around 0.3logMAR with high contrast letters, which patients with more than -2.0 dioptres of uncorrected astigmatism could not achieve. Visual acuity was further reduced by an axis of astigmatism off the vertical axis and with low contrast. The average loss of visual acuity of 1.5 lines per dioptre induced by the uncorrected astigmatism equates to approximately half the effect of spherical blur as expected from the average blur circle at the retina (Johnson and Casson, 1995). Therefore, even a relatively low amount of uncorrected astigmatism will significantly reduce visual acuity, which will further reduce ability to perform low contrast tasks. For example reduced contrast sensitivity has been shown to be associated with self restricted night driving in older adults (Freeman *et al.,* 2006), with about 20% of those in their 70's and 55% of those in their 80's not driving at night (Klein *et al.,* 2003).

Reading tasks are considered the most critical to quality of life by older individuals (Wolffsohn and Cochrane, 1999). Although less systematic than distance visual acuity (r = -0.42), reading acuity decreased a similar amount with uncorrected astigmatism power (+0.13 ± 0.07 logMAR/DC). Newspaper print (approximately 0.4 logMAR at 40cm) was only just resolvable with 2.00DC of uncorrected cylinder and made worse by the steepest axis not being in the vertical, as occurs with increasing age (Ferrer-Blasco *et al.,* 2009). Allowing for an acuity reserve of 6-18 times the threshold letter size to achieve highly fluent reading speed (Whittaker and Lovie-Kitchin, 1993), even 1.00DC of uncorrected astigmatism will affect simple everyday reading tasks. Despite reading speed being assessed with words 0.2logMAR larger than the threshold reading acuity with each lens combination, the speed was significantly reduced with higher levels of uncorrected astigmatism which will make reading tasks more difficult to perform, less pleasurable, and often leading to a reduction in independence and quality of life (Wolffsohn and Cochrane, 2000).

Difficulties with night driving and glare are reported by both elderly drivers with visual impairment and those with healthy eyes (McGregor and Chaparro, 2005). Trouble with driving at night is a commonly reported symptom in the elderly, occurring in 28.2% of drivers over the age of 50 years in the Australian Blue Mountains population study (Ives, *et al.,* 2000). Although there was no significant increase in light scatter with increasing uncorrected astigmatism power or changes in axis, this was principally due to the systematic reduction in quality of the measurements. It would therefore appear that uncorrected astigmatism negatively affects glare even though this accepted test of light scatter was unable to quantify the effect. Interestingly, while visual acuity declines with decreasing luminance and or blur, steering performance does not unless the visual field is restricted (Owens and Tyrell, 1999; Brooks *et al.,* 2005). Therefore the driving simulator findings were not unexpected. However, performance with unexpected events and poorer driving conditions such as rain and on-coming traffic headlights may still be compromised by uncorrected astigmatism.

Patients' rating of clarity was significantly reduced by increasing uncorrected astigmatic power. The patients were allowed to use their standard viewing conditions, which were kept constant between comparisons. They were also masked to the level of uncorrected astigmatism, so this was a real effect. Therefore, as well as the effect on visual function, patients were aware of their reduced vision, so uncorrected astigmatism is likely to negatively impact quality of life. Although patients could choose to improve their vision by the use of spectacles or contact lenses, they are unlikely to do this if left with just astigmatic refractive error with current improvements in biometry (Buckhurst *et al.,* 2009) or implantation of intraocular lenses that correct presbyopia (Madrid-Costa *et al.,* 2010; Sheppard *et al.,* 2010).

The main limitation to this study relates to adaptation effects known to occur after changes in the optics in from of the eye, which may have reduced the impairment measured with time. It was unrealistic to expect the patients to wear the corrections examined in the study for about a month before examining each one. Patients could have been recruited with different levels of astigmatism, but that would not have allowed comparison of different levels of uncorrected astigmatism without a huge cohort to account for individual variability. Assessment of glare with increasing astigmatic error failed to quantify any systematic effect that may have been present due to reduction in the quality of measurements as the power of astigmatism increased. Glare testing could be repeated using halometry devices (see chapter 7), to quantify the extent of glare perception. Driving simulation also did not show any compromise with astigmatic error perhaps due to peripheral vision being less sensitive to blur, as this task consisted of reacting to pedestrians crossing and braking with changes in speed. The high contrast nature of the test may have also influenced results, repeating with real driving simulations in poor weather or night conditions may better depict the typical effects of astigmatism during driving.

2.6. Conclusion

In conclusion, uncorrected astigmatism significantly compromises a patient's vision. In the long-term this is likely to lead to restricted independence, reduced quality of life and falls (Black and Wood, 2005; Lotery *et al.,* 2007). With modern intraocular lenses implanted after cataract surgery, astigmatism can easily be corrected (Buckhurst *et al.,* 2010) and modern designs show increased orientational stability. However, there is still no standard procedure for aligning toric IOLs during surgery and new imaging techniques require further refinement which will be addressed in chapter 3. The findings of this chapter show the additional cost of these 'premium' lenses is likely to be far less than the consequences of leaving them with uncorrected astigmatism. It is estimated by the Royal Society for the Prevention of Accidents (ROSPA) that one in three aged 65 years and over may experience a fall at least once a year and one in two in those over 80 years (NICE guideline for Assessment & Prevention of Falls, 2004). In 1999, fall related injuries incurred costs of £908.9 million with 63% of which was accounted by patients over 75 years. Toric intraocular lenses typically cost £500 per eye with private surgery fees reaching £2500 per eye. However if such implants were made available on the National Health Service with the option for patients to 'top up' fees to receive toric IOLs it would prove beneficial by aiding the prevention falls as well as improving driving safety. Hence, this study suggests correction of corneal astigmatism during cataract surgery and intraocular lens implantation should be the standard of care.

CHAPTER 3

The Effect of Dilation on Toric Intraocular Lens Aligning and Centring

3.1. Introduction

Astigmatism over 1.50 dioptres occurs in approximately 20% of patients presenting for cataract surgery (Ferrer-Blasco *et al.,* 2009). Although this astigmatism can be reduced by corneal or limbal relaxing incisions, toric intraocular lens implants (IOLs) give a more predictable result and can correct higher levels of astigmatism (Sun *et al.,* 2000; Mendicute *et al.,* 2009). Chapter 2 has already shown that uncorrected astigmatism can have a significant impact on the performance of daily tasks even if the mean spherical equivalent refraction is corrected, resulting in reduced quality of life. Successful toric IOL implantation requires precise and accurate marking of the orientation at which the intraocular lens is to be implanted, as misalignment by as little as 1° can result in an estimated 3.3% loss of cylindrical correction (Lane, 2006). It is reported a deviation of 30° with a toric IOL results in no correction of cylindrical power (Shimzu *et al.,* 1994) and anything greater will add to the cylindrical power requiring correction (Novis, 2000).

The axis of astigmatic orientation or horizontal axis is generally marked on the peripheral cornea or over the sclera prior to surgery to account for the cyclorotation of the eye when moving to a supine position for the surgical procedure (Smith *et al.,* 1994; 1995). Ink markings often spread due to the blink action and tear film movement, and fade with time. Even laceration markings have a finite size and rely on a surgeon's skill to be correctly located with reference to a biomicroscope slit illumination orientation or protractor increments. Markings are usually made with patients sitting at a slit-lamp biomicroscope, thus stable head positioning is critical in order to avoid misalignments due to head tilts (Wolffsohn *et al.,* 2011). There have been suggestions of using Nd:YAG laser to mark the cornea to overcome some of these issues (Bordanaba *et al.,* 2009), but head tilt again may prove a source of error. Imaging systems use conjunctival blood vessels or iris features as markers for orientation, but the robustness of this approach with variation in dilation during the imaging and surgery has not been investigated (Wolffsohn *et al.,* 2010).

During refractive surgery and cataract extraction pharmacological dilation of the pupil is required to create an adequate opening for removal of the crystalline lens and insertion of the IOL. It is generally assumed that the pupil is circular, well centred within the iris and that dilation, caused by smooth muscle in the iris, occurs symmetrically. However, the pupil is generally located slightly nasal and superior to the geometric centre of the cornea (Yang *et al.,* 2002). It has been documented that with pupil dilation there is a corresponding change in pupil centration, which is of clinical importance in ophthalmic surgery where pupil centration relative to the limbus can affect surgical outcomes (Walsh 1988; Wilson and Campbell 1992; Yang *et al.,* 2002). The eye suffers a range of regular and irregular optical aberrations which can vary between eyes (Walsh *et al.,* 1988). Both pupil dilation and decentration have been noted to increase high order aberrations within the visual system (Ivanhoff 1956; Yang *et al.,* 2002), in particular spherical aberration and coma (Wilson *et al.,* 1992), thus degrading retinal image quality. These aspects must be taken into consideration for various refractive procedures such as toric implantation, as poor centration of an IOL will give rise to further optical aberrations resulting in reduced image quality.

Various studies have been carried out in order to investigate the changes in pupil centration with changes in diameter. Walsh (1988) analysed projected photographs of light and dark adapted and pharmacologically dilated eyes of 39 subjects and found superior (0.02 ± 0.14mm) and temporal (0.03 ± 0.15mm) decentration of the pupil with pharmacologically- induced mydriasis. No systematic pattern was found with decentration in relation to the level of mydriasis, however, although the decentration measured was of small magnitude this can still impact image quality hence expressing its significance in surgery. The centration changes were also found to be similar between eyes for the majority. Wyatt (1995) found nasal and superior decentration of the pupil with *constriction* in a study of 23 subjects, through analysis of projected and digitised slit lamp photographs. The photographs were first captured in steady illumination followed by photographs of eyes in darkness after approximately 10 to 20 seconds, hence observing natural dilation. Wilson et al (1992) however found greater shifts in centration in comparison to the above studies.

More recent experimentation conducted by Yang *et al* (2002) involved monitoring pupil decentration in mesopic, photopic and pharmacologically dilated conditions using an infrared camera. High resolution images of 70 subjects were analysed and found a significant supero-temporal (0.162 ± 0.083mm) shift in the pupil centre following mydriatics. A similar shift was found when measuring dilation from photopic to scotopic conditions (0.183 ± 0.093 mm). As with the investigations carried out by Walsh (1988) and Wyatt (1995), Yang *et al* (2002) also found nasal decentration on pupil constriction, with left eyes showing greater displacement than right eyes. Vertical decentration was shown to be very slight in the superior direction (0.04mm) with drug-induced dilation. Although the changes in pupil location have generally been found to be small, greater, unpredictable shifts can still occur particularly with drug-induced mydriasis (Walsh 1988; Yang *et al.,* 2002; Wilson *et al.,* 1992) which proves a challenge for surgery.

Age and refractive error may be considered as variables which may affect the pupil location however Yang *et al* (2002) reports no such relationship exists. There is, however, a well known linear decrease in pupil size with age thus young patients may show greater shifts in pupil centre (Winn *et al* 1994; Yang *et al* 2002).

Therefore this study examined the effect of pharmaceutical dilation on conjunctival vessels and iris features and their potential as biological markers for aligning toric IOLs. In addition, the changes in pupil centration relative to the limbus that occur with various degrees of dilation were assessed.

3.2. Methods

Thirty six subjects were recruited with a mean age of 21.7 ± 2.7 years, 20 males and 16 females. All participants were healthy individuals with no ocular pathology. Exclusion criteria included no ocular abnormalities or pathology, no previous history of ocular surgery and no medication likely to affect rate or process of pupil dilation. Patients were required to maintain adequate posture as the procedure involved sitting still at a slit lamp for a duration of time.

After obtaining informed consent, intraocular pressures and anterior angle measurements were measured prior to pharmaceutical dilation to ensure suitability of individuals for the investigation. Right eyes of each subject were then pharmacologically dilated using two drops of Tropicamide 0.5% to ensure maximal dilation. Ethical approval was granted by the Aston University Ethics Committee and the study conformed to the tenets of the declaration of Helsinki.

Subjects were seated at a slit lamp where images of right eyes were taken every 2 minutes from immediately following instillation of the drops using an anterior eye imaging system attached to a CSO Elite slit lamp (*Figure 3.1*) with high pixel light sensitivity (Costruzione Strumenti Oftalmici, Scandicci, Italy). Images were captured for 30 minutes until maximal dilation was achieved (Levine, 1976; Krumholz *et al.,* 2006). Patients were instructed to keep as stable as possible during photographs to ensure clear images were captured for analysis, as movement would cause blurring and loss of detail in images.

The images were captured onto a computer linked to the imaging device, the camera exposure and image brightness were both controlled by Epsilon Lyrae software. Pairs of images were taken at each 2 minute time interval to allow for blurred images to be replaced. The pupils were illuminated by an external diffuse light source and a thin slit beam was positioned temporal to the limbus to minimise any influence on pupil diameter. At the end of the process intraocular pressure and angle measurements were repeated.

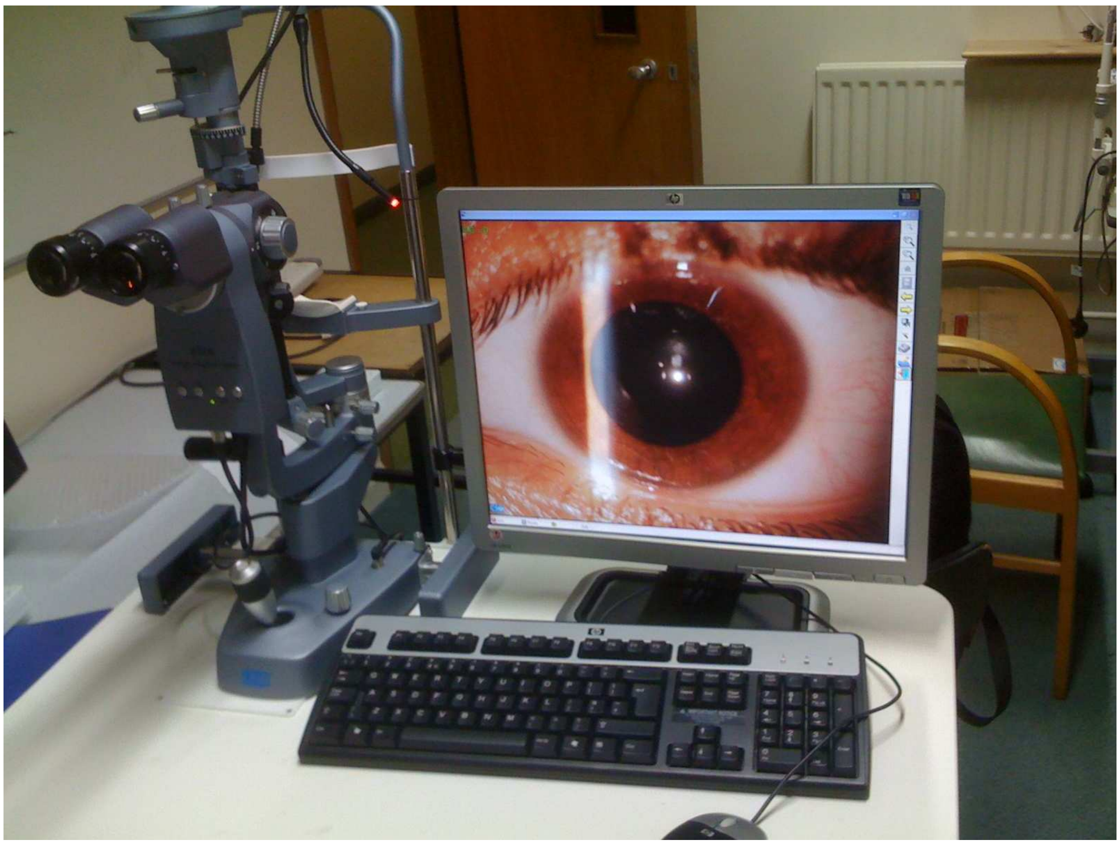


Figure 3.1: *CSO Elite Slit Lamp*

Analysis of the photographic images was then carried out using bespoke LabView™ 2010 imaging software (Wolffsohn and Buckhurst, 2010). For each subject, pairs of the most prominent conjunctival vessels were chosen horizontally separated on either side of the limbus, and using LabView™ (National Instruments Corporation, Austin, United States) the orientation of these vessels were determined by drawing a line from one vessel to the other (*Figure 3.2*).

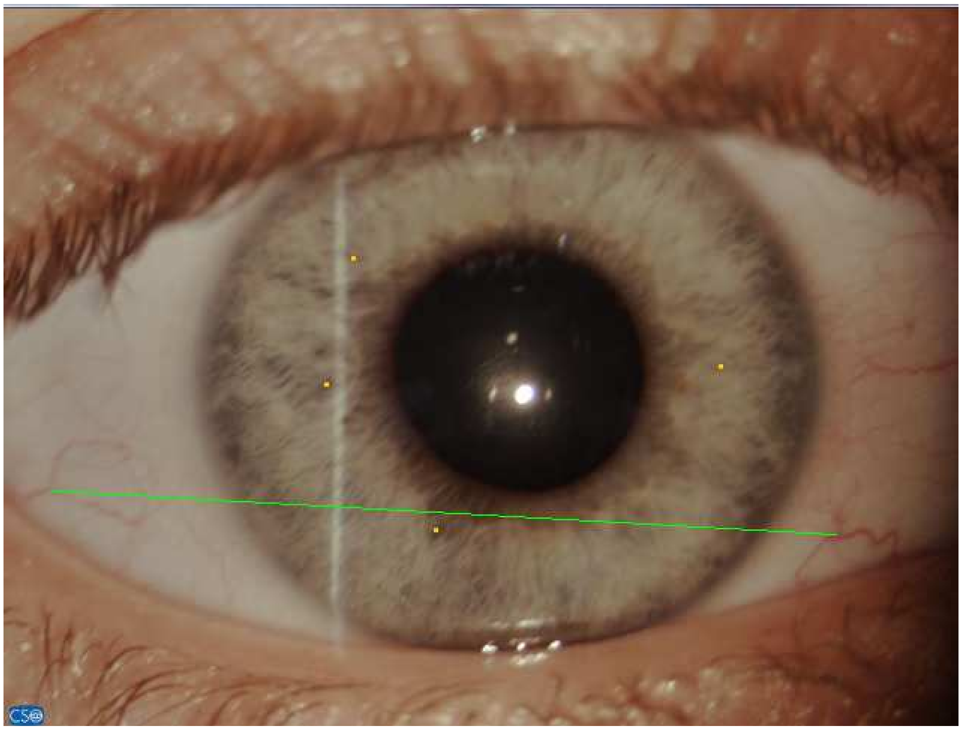


Figure 3.2: *Two conjunctival vessels chosen, connected with line for measurements*

Pairs of horizontal and vertical prominent features on the iris either side of the pupil were also selected for each participant, the orientation of which at each time point was determined by the same line drawing technique (*Figure 3.3A, B*). Ovals were drawn to fit both the pupil and limbal margins to give the respective centration as well as width and height measurements in terms of X and Y coordinates. For pupils this was measured twice per image to give an average of height and width (*Figure 3.4*).

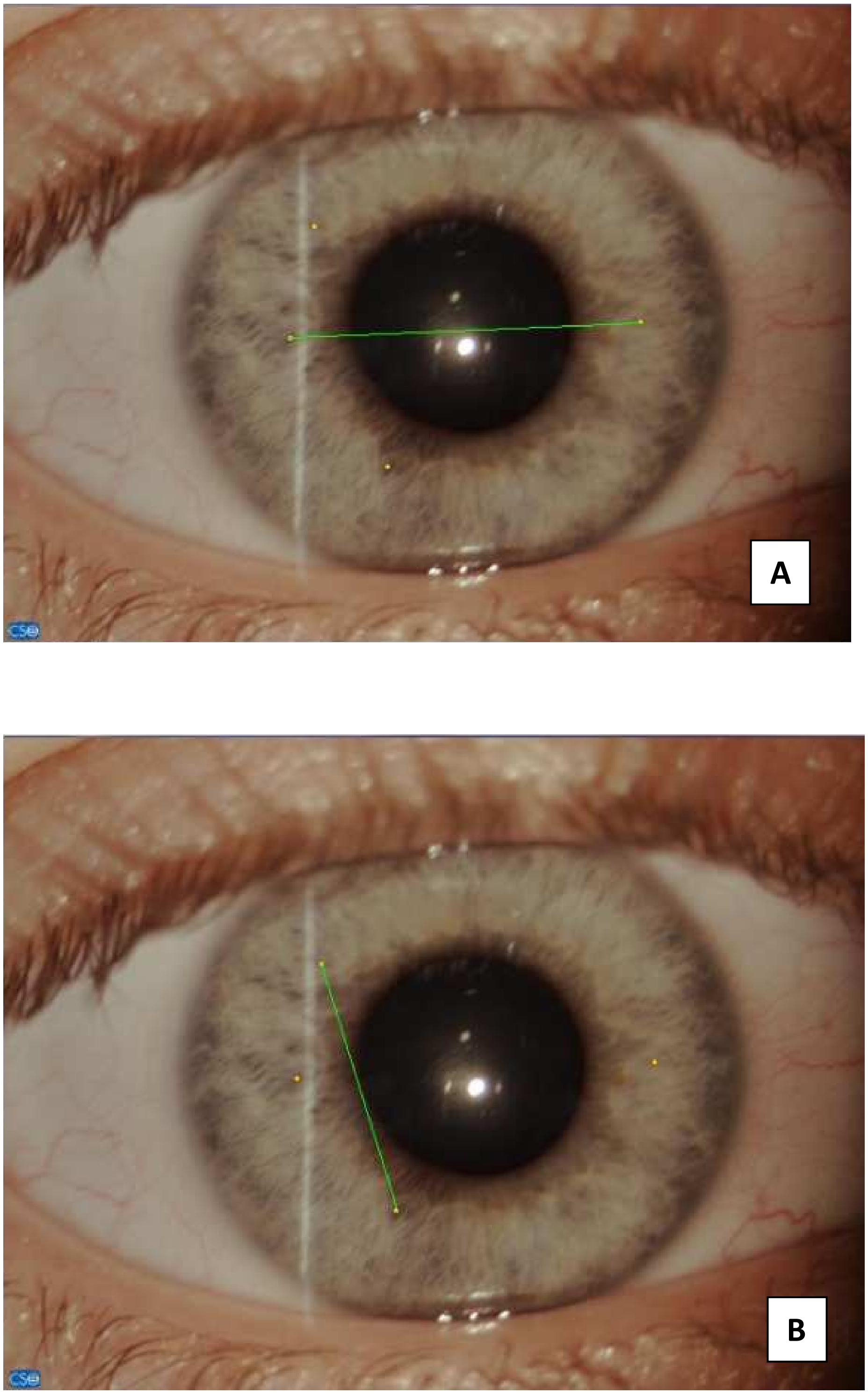


Figure 3.3:

Horizontal (A) and vertical (B) iris features connected for measurements of separation

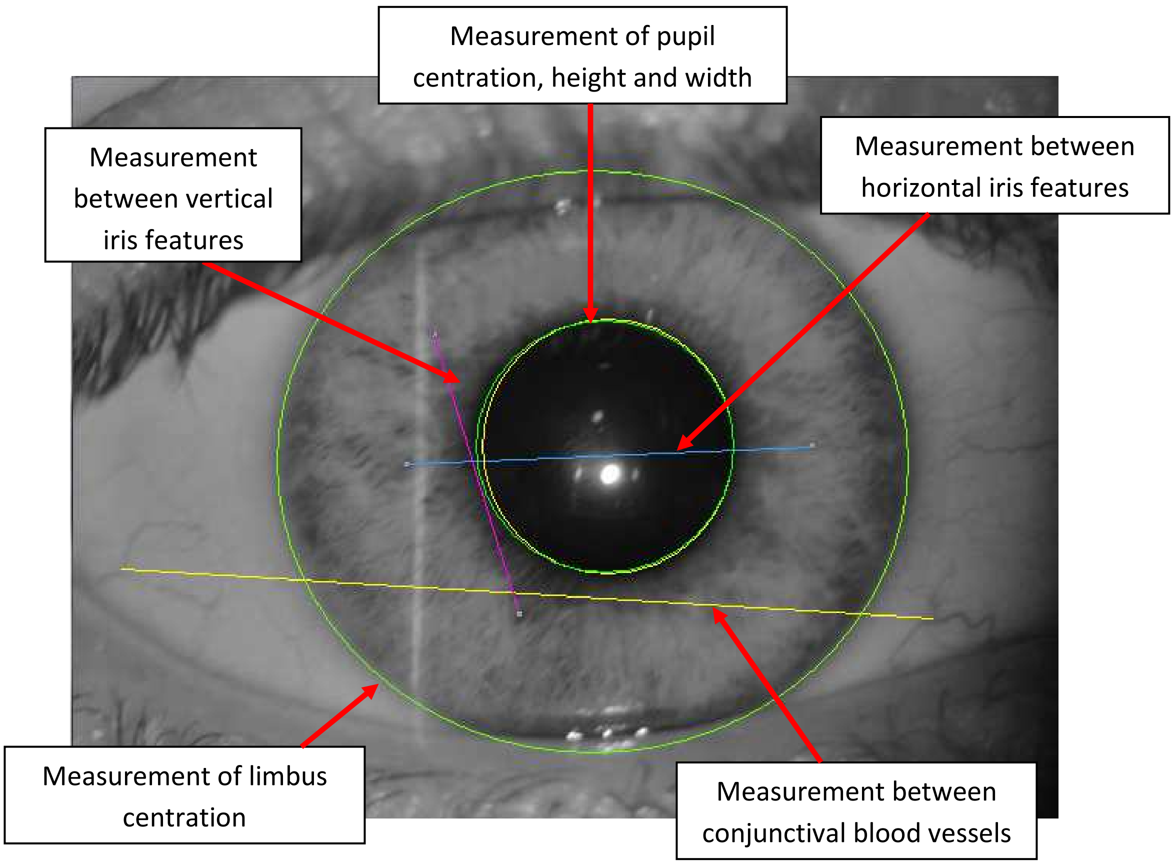


Figure 3.4: *Image analysis showing orientation lines joining horizontal conjunctival blood vessels and horizontal and vertical iris features as well as ovals fitted to the pupil and limbal edge to allow centration and width and height to be determined during dilation.*

3.3. Statistical Analysis

For repeatability purposes one randomly selected image per subject was re-analysed. As the values obtained were in pixel units a conversion factor determined from image analysing a millimetre unit ruler was applied (1 pixel = 0.01475mm) in order to convert the measurements to millimetres. Statistical analysis was then carried out to determine the significance of the results obtained.

3.4. Results

The average standard deviation of the 15 images for each subject captured every 2 minutes between dilation drug instillation and 30 minutes of limbal width (0.17 ± 0.07 mm) and height (0.21 ± 0.08 mm) and the ratio between them (0.02 ± 0.01) were similar to that of the measurement variability of repeated analysis of the same image twice (*Table 3.1*).

Table3.1: *Standard deviations of repeat analysis for the ocular measurements. N = 36.*

	Blood Vessel Orientation (^{0})	**Horiz. Iris Features (^{0})**	**Vertical Iris Features (^{0})**	**Pupil Width (mm)**	**Pupil Height (mm)**	**Limbus Width (mm)**	**Limbus Height (mm)**	**Limbal Width/Height Ratio**
SD	0.63	0.39	0.87	0.12	0.12	0.23	0.22	0.03

Hence the eye orientation and position from the slit lamp camera seems to be well controlled by the conventional slit lamp head/chin rest and the slit-lamp focusing, and no compensation of the images captured between visits based on apparent limbal dimensions was therefore applied. At the typical slit lamp to eye distance of 30cm, a 0.20mm change in limbal width (of 12.00mm) would occur from a 5mm change in slit lamp to eye distance and a 0.02mm change in limbal width to height ratio from a 11.4^o orientation change of the pupil to the camera plane.

The limbus was generally vertically oval varying little with repeat imaging at each visit (width to height ratio 1.065 ± 0.003). The pupil was essentially symmetrical (width to height ratio 1.018 ± 0.018 at baseline), and remained so with dilation (SD ± 0.013) as it increased in size in a sigmoid manner, with maximum dilation reached by approximately 25 minutes ($y = -3.594 / (1 + e^{(-(x-13.18)/3.569)})$ $r^2=0.998$; *Figure 3.5*).

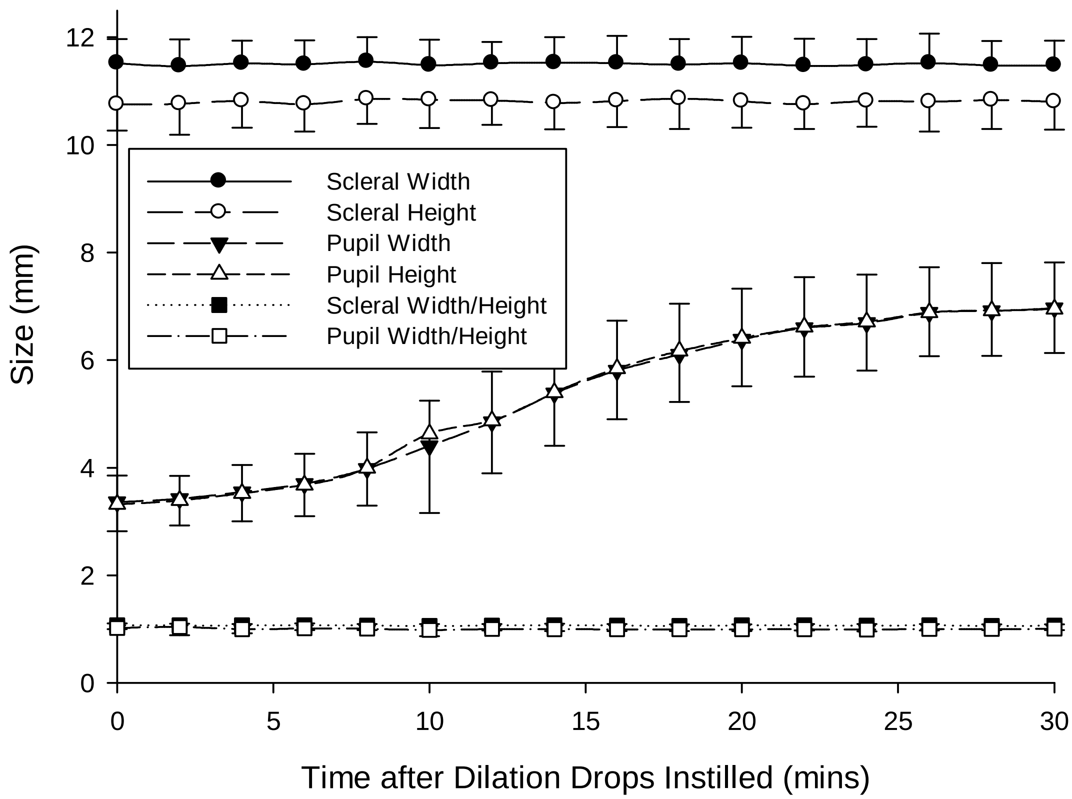


Figure 3.5: *Variations in width and height of pupil, limbus and sclera with dilation. N = 36. Error bars =1 S.D.*

Pupil dilation had no significant effect on the average change in orientation of the conjunctival blood vessels, horizontal or vertical iris features ($F = 2.95$, $p = 0.069$, *Figure 3.6*), however, the variability between subjects was much greater using iris features than conjunctival blood vessels ($F = 31.233$, $p < 0.001$; *Figure 3.6*). The change in pupil size was more strongly correlated to the change in orientation with the horizontal ($r = 0.13 \pm 0.60$) and vertical (0.18 ± 0.49) iris features than the conjunctival blood vessels ($r = 0.02 \pm 0.43$; $F = 3.149$, $p = 0.049$).

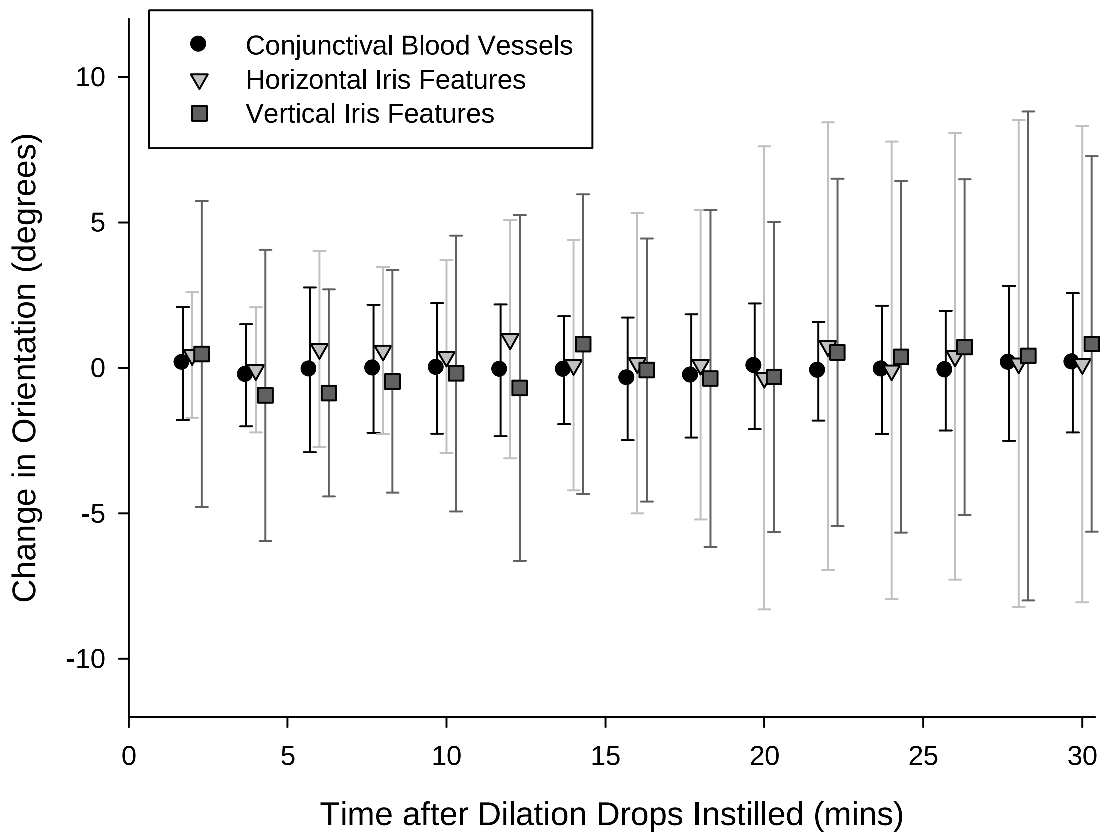


Figure 3.6: *Orientation changes of conjunctival blood vessels and iris features through the process of dilation. N = 36. Error bars = 1 S.D.*

The pupil was on average was centred superior (0.07 ± 0.09mm) and nasal (0.26 ± 0.14mm) compared to the centre of the limbus, moving superiorly with dilation with the change mainly occurring in the first 10 minutes post-dilation and some recovery from 20 minutes. Overall, there is an inferior displacement of the pupil centre (*Figure 3.7*).

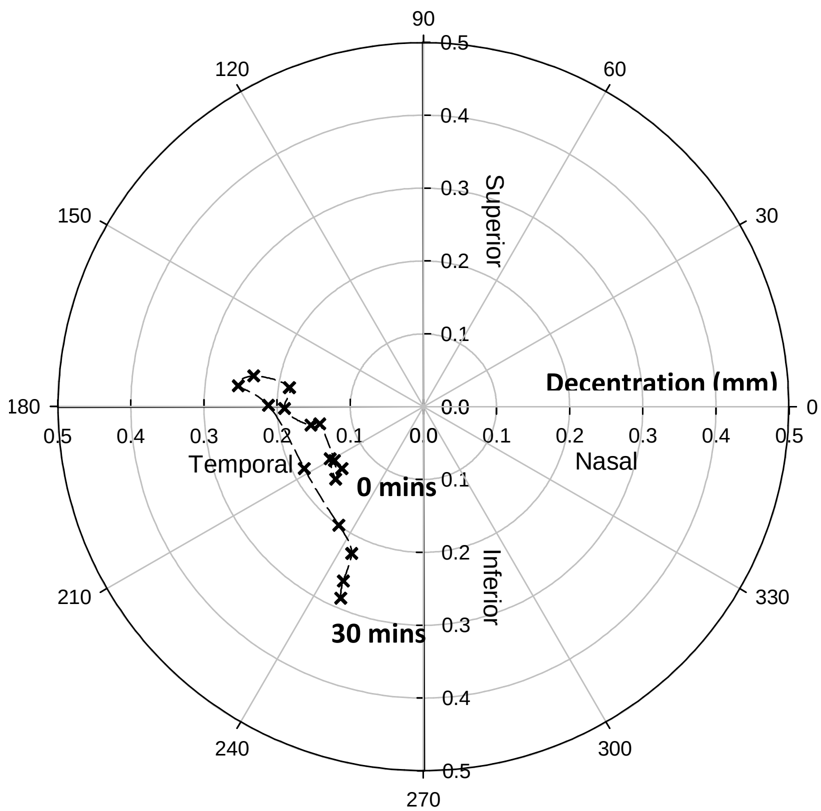


Figure 3.7: *Change in centration with dilation*

3.5. Discussion

The pupil, as expected, increased in diameter with pharmacological dilation reaching maximum dilation at approximately 25 minutes following drug instillation, the increase was generally symmetrical through the process with a sigmoidal increase in diameter. On analysis of pupil centration it was found to be located superior-nasal on average, moving inferior upon dilation, which coincides with previous studies of pupil centration (Walsh, 1988; Wyatt, 1995; Yang *et al.,* 2002). It is possible that the changes in pupil centration may be smaller with physiological than pharmacological dilation (Yang *et al,* 2002), but the intraocular lens is implanted under pharmacological dilation so these pupil centration changes need to be considered. Previous research has shown these changes are not age dependant and hence the use of young subjects should not have influenced this conclusion. Non-linearity of the pupil was calculated as 0.018 which corresponds to that found by Wyatt (1995) reporting 0.017 in dark conditions and 0.016 in light conditions.

Analysis of limbus height and width showed good repeatability over time, similar to that found on repeat analysis of the same images a second time. Therefore, this suggests there is adequate control of eye orientation using the head and chin rest of slit lamp with minimal effect from head tilt. The limbus remained generally oval in the horizontal plane which varied little upon repeat measurements. As surgeons generally use the pupil rather than the limbus to judge centration, such findings confirm the change in pupil centration when the eye is restored to physiological stimulation must be taken into consideration for surgery requiring dilation, particularly LASIK refractive surgery as ablation of the cornea must be confined to the optical zone. Ablation beyond this area can lead to glare, haloes and ghost images, hence resulting in an unsuccessful outcome (Yang *et al.,* 2002) and dissatisfaction from the patient.

Previous research has shown image analysis of lens rotation to be more robust than subjective rating, and the use of conjunctival blood vessels or iris features to allow for head rotation further improves reliability (Wolffsohn and Buckhurst, 2010). Although dilation of the pupil had no effect on the average change in orientation of blood vessels and iris features, the variability of iris features with dilation was much greater in comparison to conjunctival blood vessels. The conjunctival blood vessels therefore prove to be better markers for orientation and hence provide surgeons with anatomical markers that can be used for various procedures.

Studies carried out to investigate the changes in pupil centration with diameter, generally report a superior-temporal shift in pupil centre with pharmaceutically induced mydriasis and inferior-temporal or temporal with light induced mydriasis of magnitude less than 0.2mm, which is only related to pupil size for the latter (Walsh, 1988; Wyatt, 1995; Yang *et al.,* 2002). However, the effect of different degrees of dilation on pupil centration has not previously been assessed. This study showed a similar inferior centration shift finding with pharmaceutical dilation to that previously found with light induced mydriasis, although there was a counter movement superiorly from 20 minutes onwards. While the study was performed on younger adults to allow a wide dilation change to be imaged, age does not appear to affect pupil centration (Yang *et al.,* 2002), although non-linearities in pupil shape increase with age (Wyatt, 1995).

The limitation in this study was evaluation of only young subjects which may be found to differ if compared to older individuals. Also, the outcomes of the investigation were limited to the quality of images obtained; despite capturing two images for each stage of dilation some images presented difficulty in analysis. Hence more robust instrumentation for imaging the anterior eye and IOL should be designed and evaluated to support researchers and surgeons alike.

3.6. Conclusion

In conclusion, it is well documented that shifts in pupil centration occur with pharmacological dilation, which need to be considered for any type of refractive surgery to in order to avoid an unsuccessful outcome. The current study supports existing knowledge of this change in pupil location through dilation and has established conjunctival blood vessels as better markers for correcting the alignment of toric IOLs and compensating for head rotation compared to using iris features.

Hence, the pupil position may significantly influence the surgical outcome of premium IOLs due to the complexity of their optics through misalignment and increases in aberrations, which will be discussed further in the following chapter. The effect of modern IOL surgery on the pupil and long term changes in pupil centration relative to the limbus and IOL have not previously been considered as a potential factor in the visual performance of premium IOLs. The next chapter therefore aims to research the significance of this aspect of premium IOL optimisation.

CHAPTER 4

Stability of Pupil Dilation Following Cataract Surgery

4.1. Introduction

Various refractive surgical procedures, such as implantation of intraocular lenses, require pharmacological dilation of the pupil. It is well established, however, that the location of the pupil centre shifts with dilation (Walsh 1988; Wilson *et al*., 1992; Yang *et al*., 2002,) and as discussed in the previous chapter such decentration may lead to undesirable outcomes in refractive surgery.

The pupil is the entrance point for light approaching the visual system which regulates retinal illumination by changes in its diameter. Pupil diameter is controlled by smooth muscles in the iris; the sphincter pupillae located within the stroma of the iris and dilator pupillae radiating from the iris root into the stroma (Remington, 2005). Pupil size is affected by various factors such as; level of illumination, age, accommodation and emotions (Winn *et al.,* 1994).

Generally, the eye exhibits a range of optical aberrations (Walsh *et al.,* 1988) with increases in pupil diameter and decentration from the visual axis having been shown to increase high-order aberrations (Ivanhoff 1956; Yang *et al.,* 2002; Campbell *et al.,* 1966; Artal 1990; Liang *et al.,* 1997; Kasper *et al.,* 2006; Castejon-Mochon *et al.,* 2002; Wang *et al.,* 2003) such as spherical aberration and coma (Wilson *et al.,* 1992). High-order aberrations (HOAs) cause various visual symptoms for example, spherical aberration may form starburst and glare, whilst horizontal coma can lead to monocular diplopia (Chalita *et al.,* 2003, 2004). Optical quality is reduced with spherical aberration and often manifests as a reduction in contrast sensitivity (McLellan *et al.,* 2001; Nio *et al.,* 2000). Sakai *et al* (2007) demonstrated the correlation between pupil size with HOAs and residual astigmatism suggesting that the pupil adjusts accordingly to optimize retinal image quality in varying luminance levels.

Pupil decentration can lead to ablation outside of the optical zone in keratorefractive procedures resulting in halos, glare and some reports of reduced contrast sensitivity (Pande and Hillman, 1993). It is therefore plausible that decentration of a dilated pupil may lead to misalignment of an intraocular lens (IOL) affecting the visual outcome and degrading the retinal image, particularly with advanced optical designs such as the optics on multifocal and toric intraocular lenses.

Previous studies have indicated greater shifts in pupil centration with pharmacologically, rather than physiologically, induced dilation (Yang *et al.,* 2002). The general finding of temporal movement of the pupil centre with slight vertical shifts have been documented (Walsh *et al.,* 1988; Yang *et al.,* 2002; Wyatt 1995). Pupil decentration may be of particular concern in younger patients requiring refractive surgery, such as for congenital cataracts or when electing for refractive lens exchange, as larger pupils have shown greater degradation of M.T.F (Modular Transfer Function) by Walsh and Charman (1988).

Misalignment of a toric intraocular lens results in no correction of the cylinder and if great enough may even add to the cylindrical power (Shimzu *et al.,* 1994). Toric IOLs are susceptible to rotational instability (Novis, 2000) and if coupled with initial misalignment during surgery, may result in a very poor surgical outcome with substantial patient dissatisfaction.

Multifocal IOLs manipulate aberrations to enhance the depth of focus of the eye, but can give rise to photic phenomena (Leyland and Zinicola, 2003; Hayayshi *et al.,* 2009; Steinert, 2000). As IOL position and tilt may adversely affect the effectiveness of the IOL it could be assumed that there may be an association between the centration of multifocal intraocular lenses and dysphotopsia.

Age-related lenticular changes lead to increased high-order aberrations (HOAs) in later life, particularly spherical aberration (Nio *et al.,* 2002; McLellan *et al.,* 2001). In the young eye the positive corneal aberration is reduced by the negative aberration of the crystalline lens. Following cataract surgery there is an increase in such aberration as often the natural lens is replaced by a spherical monofocal lens which exhibit higher degrees of optical aberrations (De Castro *et al.,* 2007). For these reasons aspheric designs have been developed to improve the visual outcome by incorporating negative spherical aberration within the lens. The effect of these aspheric lenses, however, may be lost by IOL displacement as shown by many studies; for example Mckelvie *et al* (2011) showed pupil size had the most affect on HOA in their investigation followed by IOL decentration, stating 0.5mm of decentration can vastly affect the performance of an aspheric IOL particularly those which incorporate higher levels of negative asphericity. The authors demonstrated that 0.5mm decentration of an IOL, with -0.27µm of negative spherical aberration, would increase HOA by 48% which would increase to 80% with 1.5mm of decentration. Performance of aspheric multifocal IOLs are also jeopardized by decentration exceeding 0.5mm (Atchison 1991; Altman *et al.,* 2005).

Coma also increases with decentration and tilt, as shown by optical bench tests by Epigg *et al* (2009) and Pieh *et al* (2009), which impairs visual quality. Despite these claims, some studies have not found any significant change in HOAs with decentration and tilt of an aspheric IOL such as that of Choi *et al* (2010) which perhaps may have been due to their small sample size of only 32 participants, however, another study by Baumeister *et al.,* (2009) also did not find any correlation between image quality and decentration of aspheric IOLs.

Holladay *et al* (2002) stated if an aspheric IOL was centred within 0.4mm and tilted less than 7° its optical performance would surpass that of a monofocal while Lopez-Gil *et al* (2007) suggest for optimum performance an IOL should be centred in line with the visual axis. It is therefore clear that negative spherical aberration can be altered by IOL tilt and decentration the effect of which is greater with higher levels of asphericity inducing higher amounts of HOAs.

The result of decentration or tilting of IOLs that provide negative spherical aberration may be observed as impairment of contrast sensitivity (Baumeister *et al.,* 2005). It has been shown by Pepose *et al* (2005) an increase of 1µm in HOAs can reduce photopic contrast sensitivity by 2.5 logarithm of min angle of resolution and a reduction in mesopic contrast sensitivity of 12 logarithm min angle of resolution. In addition, Epigg *et al* (2009) investigated six IOLs and reported poor MTF measures with decentration with a 3mm pupil for the five aspheric IOLs, whereas measures with the spherical IOL were relatively unaffected. For a larger pupil of 4.5mm decentration gave rise to horizontal coma, astigmatism and defocus, with the performance of the Tecnis Z9000 IOL being most affected by decentration. Aspheric lenses, particularly, aberration-correcting IOLs are thus more vulnerable to tilt and decentration despite their aim of providing better image quality. Conversely, aberration-free IOLs are less affected by decentration, the use of which is suggested where centration could be suboptimal (Eppig *et al.,* 2009). Many premium IOLs incorporate asphericity into their design and hence may be vulnerable to impairment of contrast sensitivity, which in the case of multifocal IOLs may exacerbate the already reported reduced contrast sensitivity.

Misplacement of IOLs may also affect refractive error; computer modelling by Korynta *et al* (1999) indicated a shift towards myopia and oblique astigmatism with IOL decentration, but the resultant effect was dependent on the amount of dislocation. Earlier investigations by Atchison (1989) had already established that decentration considerably affected refractive errors, which were calculated to be proportional to the square of decentration. In addition, it was found coma-like aberration and astigmatism affected the retinal image by IOL displacement and that larger pupils (≥4mm) suffered more from spherical aberration, whilst smaller pupils were affected principally by astigmatism (Atchison, 1989).

It is suggested that in addition to surgical technique, IOL haptic design may also influence stability of an IOL (Epigg *et al.,* 2009). Haptics made from PMMA have been reported to give better stability (Ohmi *et al.,* 1995; Gallagher *et al.,* 1999), although Baumeister *et al* (2005) found no such difference between haptic materials over a 12 month period. Post-operative intraocular lens rotation tends to occur during the earlier postoperative stages (Rushwurm *et al*., 2000) as a result of friction between lens haptics and capsular bag, instability of the anterior chamber due to intraocular pressure or ocular trauma, IOL design, the level of fibrosis or compression of haptics as shrinkage of the capsular bag occurs (Buckhurst *et al.,* 2010). Post-operative rotation combined with initial displacement of the IOL due to pupil decentration can lead to various visual symptoms and thus a poor surgical outcome. In extreme cases dislocated IOLs may have to be explanted, putting unnecessary constraints on financial resources and possibly increasing risks of endophthalmitis. Repositioning a rotated IOL, such as a toric lens is possible, however may further raise complications such as; CMO, capsular tears and endophthalmitis and thus is favourable to avoid (Sun *et al.,* 2000).

Regardless of the direction of pupil decentration, the resultant aberration will degrade the quality of the retinal image and affect spatial vision (Walsh and Charman 1988; Thibos 1987). Even small pupil displacements may induce significant levels of aberrations (Rynders *et al*., 1995). There is now more interest developing in IOL tilt and decentration as development of IOLs begins to widen attention to broader aspects of IOL design and focus more on correcting HOAs in addition to refractive error (Mester *et al.,* 2003).

There is little literature on the effects of cataract surgery on the pupil; however Gibbens *et al* (1989) did carry out an investigation to examine the effects of post-operative pupil dilation with intracapsular cataract extraction (ICCE) and extracapsular cataract extraction (ECCE) surgical procedures. A significantly smaller post-operative pupil size was noted on dilation with both surgical procedures, but the location of the pupil was not assessed. The effect of more recent cataract extraction procedures on the stability and post-operative location of the pupil has not yet been explored within the literature therefore; the purpose of the present study was to investigate the changes in size and centration stability of the pupil six months following cataract surgery and intraocular lens (IOL) implantation.

4.2. Methods

Two hundred and four patients were implanted monocularly with the fifth generation Akreos AO aspheric IOL (Bausch and Lomb, Rochester, New York) in one eye at six hospital sites across Europe. Inclusion criteria included age-related cataract amenable to treatment with standard phacoemulsification and IOL implantation, and pupils which could be dilated to at least 5mm. Subjects were aged 67.6 ± 7.9 years (range 51 to 89 years) and 65% were female.

The acrylic, hydrophilic lens has a 6 mm optic with a 360° posterior square edge barrier attached to 11 mm closed loop haptics. The optic has aspheric surfaces aiming to induce no IOL aberrations. A 5.5 mm continuous curvilinear capsulotomy was used through which phacoemulsification was performed. Once the capsular bag was filled with a viscoelastic substance, the lens was inserted using an *Akreos* single use insertion device through a 2.8 mm incision and the viscoelastic device aspirated from in front and behind the lens.

Patients were dilated using phenylephrine 2.5% and tropicamide 1.0% at the operative visit and the following four post-operative appointments. These appointments were conducted 0, 1-2, 7-14, 30-60 and 120-180 days after IOL implantation. The intraocular lens was imaged at 10x magnification in retroilluminantion using a CSO SL-990 digital slit-lamp biomicroscope

(Construzione Strumenti Oftalmici, Florence, Italy). Informed consent was obtained from all participants prior to lens implantation and the study was approved by ethical committees at each of the sites.

The centre of three ovals overlaid to circumscribe the IOL optic edge, the pupil margin and the limbus, were compared to determine the IOL centration (*Figure 4.1*). Pupil diameter and height were taken from the pupil oval dimensions. This technique has previously been evaluated and showed excellent repeatability (Wolffsohn and Buckhurst, 2010).

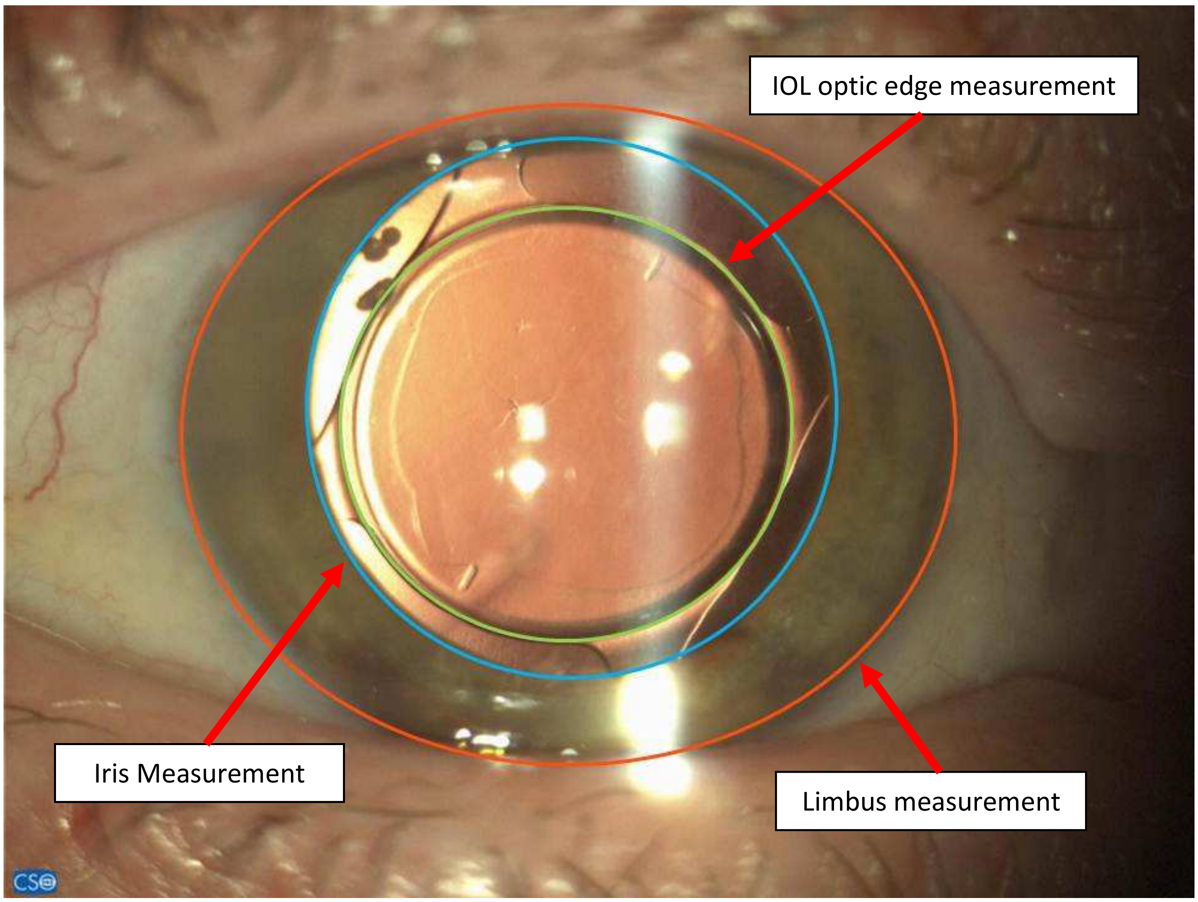


Figure 4.1: *Measurement of pupil, limbus and IOL edge*

4.3. Statistical Analysis

The IOL and pupil centration with respect to the limbus at each visit was subtracted from the values immediately after surgery to assess decentration. Repeated measure analysis of variance was used to assess locational stability between visits.

4.4. Results

There was a significant inferior shift in pupil centration with time after cataract surgery ($F=2.953$, $p=0.02$), but no significant change in horizontal centration ($F=1.010$, $p=0.4$). Intraocular lens centration was stable with respect to the limbus (width $F=0.483$, $p=0.75$; height $F=0.282$, $p=0.89$), but was decentred relative to the pupil vertically ($F=7.672$, $p<0.001$), but not horizontally ($F=1.120$, $p=0.35$; *Figure4.2*) thus indicating a change in centration.

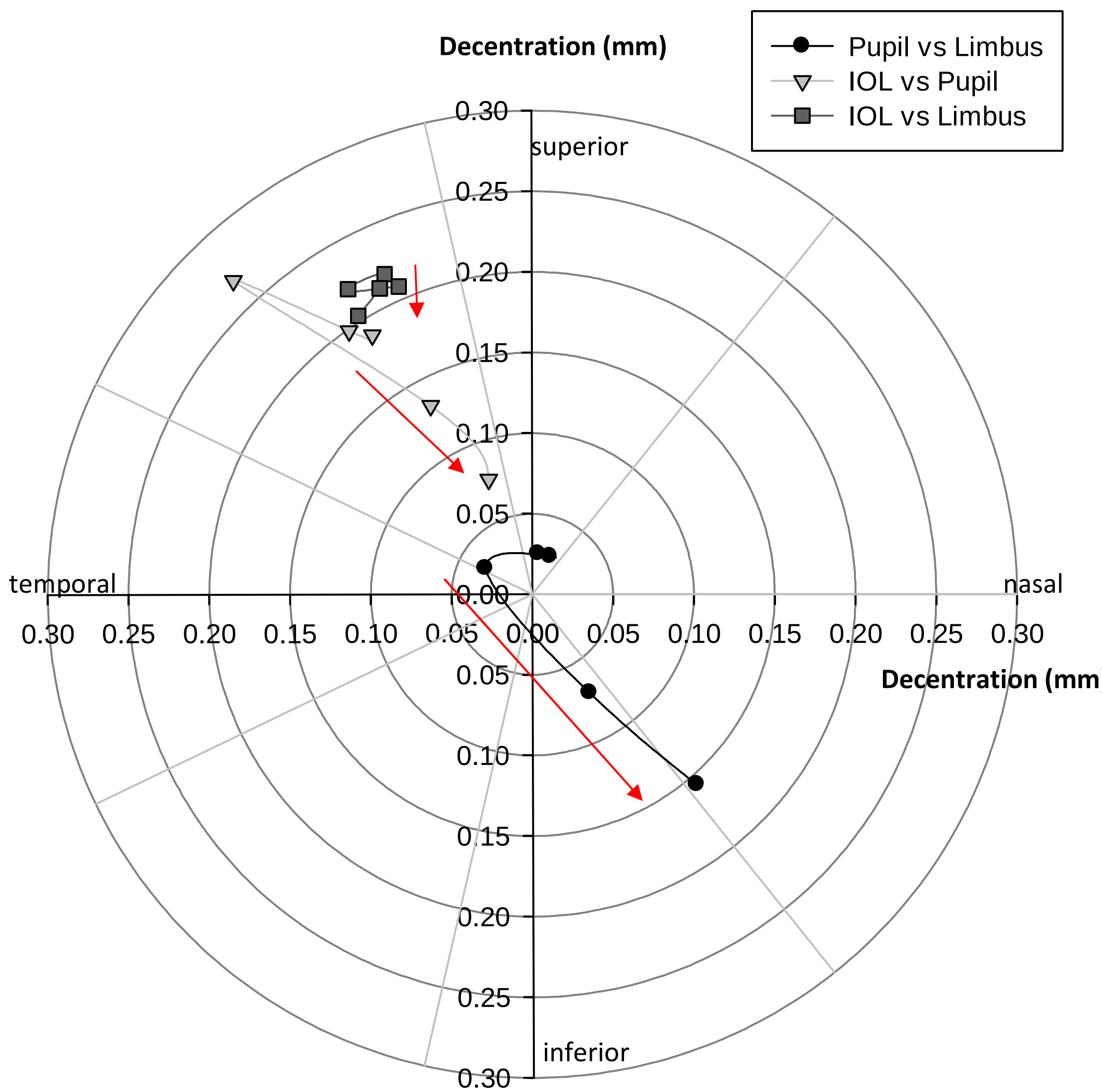


Figure 4.2: *IOL, dilated pupil and limbal centration relative to each other with time post-cataract surgery. Pupil centration becomes increasingly inferior relative to the limbus and IOL. N = 204.*
(Red arrows indicate direction of movement on subsequent visits)

Pupil width ($F=32.476$, $p<0.001$) and height ($F=35.167$, $p<0.001$) were significantly larger with dilation immediately after surgery than at subsequent dilations *(Figure 4.3).* The ratio between pupil width and height was close to 1.0, but also altered with time after surgery ($F=36.009$, $p<0.001$), becoming more vertically oval.

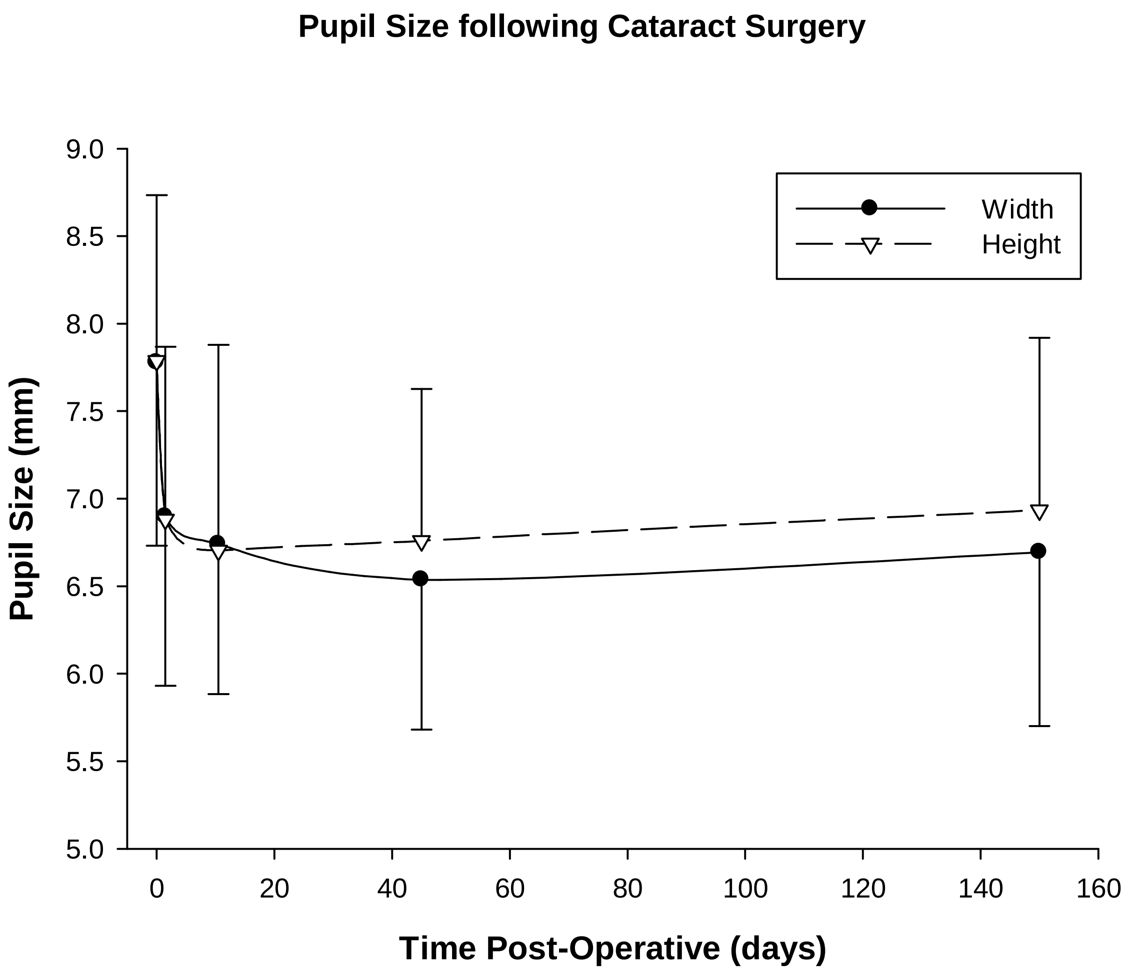


Figure 4.3: *Dilated pupil width and height with time post cataract surgery.*

N = 204. Error bars = 1 S.D.

4.5. Discussion

The results have shown a significant inferior shift in pupil centration following cataract surgery. As there was no relative change with time between the IOL and limbus, this suggests that the IOL is stable within the eye, but the pupil dilator pupillae or iris tissue has been damaged in some way as the shift was only in one meridian. The significant decrease in post-operative pupil diameter with dilation found with time may indicate additional sphincter muscular damage.

An earlier investigation by Gibbens *et al* (1989) similarly assessed the pupil following ECCE as well as ICCE, as it was stated at the time clinicians believed the aphakic pupil did not dilate as well as pre-operatively. In scotopic conditions the pupil diameter was on average 0.3mm less than pre-operatively whereas in photopic conditions it constricted less and was larger by 0.3mm, suggesting possible damage to the iris which reduced its mobility. The diameter of the aphakic pupils implanted with an IOL were also reduced by 0.9mm when dilated with Tropicamide 0.5% and Phenylephrine 10% similar to the horizontal pupil dilation reduction found in this study. Gibbens and colleagues (1989) found the pupil size reduction with repeat dilation after surgery did not occur in aphakic eyes suggesting the damage was due to IOL implantation, rather than the cataract removal, although surgical techniques and IOL materials and designs since have changed.

Understandably, with Gibbens *et al* (1989) study, ICCE without IOL implantation reduced the pupil diameter most, as this involves the removal of the entire lens cavity and capsule and hence the most disturbance to the eye. No ICCE with IOL implantation group were examined so it is not possible to tell whether the IOL would have contributed further damage in this scenario.

Decentration and tilt of IOLs may also occur following cataract surgery for various reasons such as; capsule contraction, asymmetric bag and sulcus fixation or capsular tear (Jung *et al.,* 2000), surgical technique, residual cortical material, IOL properties, asymmetric haptic fixation or haptic location (Cabellero *et al.,* 1991; Hansen *et al.,* 1988; Akkin *et al.,* 1994; Kimura *et al.,* 1996). The incidence of such occurrences has reduced since the introduction of phacoemulsification and development of more stable IOLs. However, combined with pupil decentration there may be substantial impairment of visual quality.

The apparent inferior shift in the pupil centre following cataract surgery may account for various visual phenomena with multifocal IOLs. Many studies have shown a general increase in high-order aberrations following cataract surgery (Hayashi *et al*., 2000; Barbero *et al*., 2003; Guirao *et al*., 2004), perhaps contributed to by poor centration of IOLs, reducing contrast sensitivity and causing undesirable refractive errors. Better surgical technique of aligning IOLs is therefore required in order to prevent dislocation cases (Mutlu *et al*., 2005). Visual phenomena do tend to lessen in subjective significance with time (Vaquero-Ruano *et al.,* 1998), but this may be due to adaptation to the aberrations and their effects rather than them resolving with time. Restricted pupil diameters following surgical intervention may also affect the treatment of the peripheral retina, should it be required, and the effectiveness of premium IOLs such as; multifocal designs if annular zones are not adequately exposed.

The main limitation of the present investigation was lack of pre-operative pupil diameters, measurements were only taken on the date of surgery and on post-operative visits. Knowledge of the average pupil diameters before surgery would provide confirmation of reductions of pupil mobility and hence iris damage. However it should be noted the differences that were presented at subsequent visits may be attributed to increased corneal permeability at the time of surgery.

4.6. Conclusion

In conclusion, this research confirms that when a pupil is pharmacologically dilated for cataract surgery it cannot be used as a satisfactory guide for centration (Melki *et al*., 2011). The limbus is a better guide although the pre-dilation pupil decentration relative to the limbus also needs to be taken into account when positioning an IOL. Such knowledge becomes even more critical when premium IOLs are to be implanted because of their more complex optical designs, which can cause a significant reduction in visual quality if they are not perfectly centred. In addition, research is warranted into the development of new surgical IOL implantation techniques and IOL materials and designs that do not impair the dilation response.

Premium IOLs are becoming of growing interest in refractive surgery and not just for optimising distance vision following cataract surgery. Patients are continuously seeking for possible solutions from practitioners to presbyopia. In order to advise patients of their suitability for refractive lens exchange and what factors influence when it might be needed, a better understanding of the risk factors for presbyopia is required and this is explored in chapter 5.

CHAPTER 5

Amplitude of Accommodation & Lifestyle –

Implications for Multifocal and Accommodating IOLs

5.1. Introduction

Presbyopia is recognized as the most common ocular change occurring in middle age (Weale, 2003). The decline in amplitude of accommodation with age is well documented within literature, however, the rate of decline and onset of presbyopia for individuals varies and may be influenced by various health and environmental factors such as nutrition, climate, altitude, ethnicity and physical stature (Kragha, 1985; Kragha and Hofstetter, 1986).

Both presbyopia and cataracts occur with an ageing lens and tend to develop much earlier in populations in warmer climates (Miranda, 1979; 1980). It could be assumed that the factors increasing the development of senile cataracts may also be factors accelerating presbyopia, such that presbyopia may be the initial stage in the development of senile cataracts. Higher environmental temperature has been noted as possibly accelerating the onset of presbyopia by some authors (Kragha and Hofstetter, 1986). An inverse relationship between environmental temperature and onset of presbyopia has been demonstrated through investigations by Weale (1981a, b) and Miranda (1979) with correlation coefficients of -0.89 and -0.85 respectively. However Kragha and Hofstetter (1986) explain this relationship to be of self-selection bias and conversely reported no significant differences in bifocal additions prescribed across North and Central America, with a range of average temperatures between -7℃ and 26℃. An earlier inve stigation by Kragha (1985) on bifocal additions prescribed to patients in Nigeria showed the influence of temperature on accommodation to only just approach significance (p= 0.051, correlation coefficient -0.44), although the additions prescribed to females were significantly higher compared to males, explained to be as a result of the smaller stature of females and hence shorter working distances used rather than actual difference in accommodative ability. More recent studies, however, show females exhibit presbyopia earlier due to possible hormonal differences (Nirmalan *et al.,* 2006; Pointer 1995; Mukesh *et al.,* 2006). Women are also considered to have a higher incidence of developing cataracts as shown by the Beaver Dam Study (Klein *et al.,* 1998) and Barbados Eye Study (Leske *et al.,* 2000) although reasons for this are unclear. Other comparisons of near additions include that of Hofstetter (1968), who showed additions prescribed to patients in Fiji and Ghana were on average 0.50 dioptres higher than prescribed to Europeans of a similar age profile.

Rambo (1953) reported variance in the age of presbyopia onset with geographical location; it was documented on average as 40 years in Iran, India, Iraq, Arabia and Cuba whereas in Italy it was typically 42-43 years, but occurred much later in Sweden and Norway at 48 years of age, indicating a much earlier onset in regions closer to the equator. Similarly, Ong (1981) found presbyopia to occur earlier in southeastern Asian refugees of around 42 years. Geographical data collected by Miranda (1980) also shows a negative correlation in the Western and Eastern hemispheres, whereby presbyopia onset occurred earlier in regions of warmer climate. Differences may also occur within regions, particularly with coastal areas where presbyopia seems to occur earlier than in mountainous areas of that same region (Miranda, 1979). Variations in the findings of these studies of climate and accommodation may perhaps be due to the lack of definition of presbyopia, making comparisons between them difficult (Kragha, 1985). A study in Tanzania, where presbyopia was defined to be the inability to read N8 text at 40 centimetres with distance correction and improvement using an additional lens, found 61.7% in the population of 40 year olds and older to be presbyopic (Burke *et al.,* 2006). A similar study in Nigeria, but without a clear description of presbyopia, reported a prevalence of only 33% (Nwosu, 1998).

Ultraviolet (UV) radiation is a well-known factor contributing to the aging of the human body (Stevens and Bergmanson, 1989). For the eye, radiation between 310-400nm affects the crystalline lens (Miranda, 1979) increasing the risk of cataract development with prolonged exposure (Stevens and Bergmanson, 1989; Bergmanson and Söderberg, 1995; Roberts, 2011). It is therefore reasonable to assume that UV light can affect an individual's amplitude of accommodation and its rate of decline. Health is another aspect which can greatly affect amplitude of accommodation. Reports of conditions such as diabetes and Human Immunodeficiency Virus (HIV) have been associated with reduced amplitudes of accommodation (Newsome, 1989; Westcott *et al.,* 2001). The effect seems to be more pronounced in younger patients aged between 25-29 years; it is perhaps less noticeable in older age groups due to a significant decrease in amplitude already having taken place (Westcott *et al.,* 2001). The pathological processes in HIV infection may accelerate the changes associated with the aging of the crystalline lens through possible autonomic dysfunction (Westcott *et al.,* 2001). Comparisons of young insulin-dependent diabetic patients and non-diabetic patients have also shown reductions in pull-down measures of accommodation with diabetes (Moss *et al.,* 1987) which may be associated with hypoxia (Berens *et al.,* 1932). Duane (1925) had also noted diabetes as a possible factor reducing the amplitude of accommodation.

Most studies discussed above, considering the environmental influences on accommodation, have based their investigations on one main factor. Jain *et al* (1982) however, investigated a variety of factors possibly contributing to onset of presbyopia in an Indian population, including; temperature, UV radiation, diet and exposure to toxic substances. Approximately one-third (36%) of the population studied were found to enter presbyopia at 38 years of age or younger. Patients within rural areas showed earlier onset of presbyopia, possibly due to greater UV exposure which was not quantified in the study. A low dietary intake of amino acids was also associated with reduced levels of accommodation and earlier onset of presbyopia. Furthermore, the study noted the effect of hair dye on earlier onset of presbyopia in 4% of patients, which was supported by previous work by Jain *et al* (1979) where lenticular changes occurred in 89% and presbyopia in 7% of 200 patients using hair dye.

Specific vitamins or minerals have not been associated with presbyopia, however levels of antioxidants have been linked with cataracts particularly vitamin C, low levels of which have been noted in a population with a high prevalence of cataracts (Dherani *et al.,* 2008). Levels of carotenoids (lutein, zeaxanthin, carotenes and lycopene) are also thought to have protective effects on the crystalline lens (Dherani *et al.,* 2008). Caffeine intake can increase levels of accommodation within 30 minutes of consumption, the effect of which slowly reduces after 30 minutes (Ajayi and George, 2007), although long-term effects have not been investigated. Lifestyle habits such as long-term excessive alcohol intake and smoking may also bear significance on amplitude of accommodation and presbyopia. Subjective monocular measurements have shown reduced accommodation in alcoholics when compared to controls particularly in younger individuals, the effect being sustained even following a recovery period (Campbell *et al.,* 2001). The onset of presbyopia with prolonged higher alcohol consumption may therefore occur much earlier than anticipated. Smoking may be associated with lenticular changes, as this has been described as a possible risk factor in developing nuclear opacities (Mukesh *et al.,* 2006; Christen 1992; Hiller *et al.,* 1997; Hankinson *et al.,* 1992). The processes by which smoking effects the crystalline lens requires more research, however it is proposed that plasma concentrations which maintain transparency are interfered with (Christen *et al.,* 1992). Other explanations include excessive oxidative stress leading to cellular DNA damage (Kleiman and Spector, 1993).

As part of the World Health Organisation Vision 2020 initiative presbyopia is not recognised as a refractive error, however increases in the elderly population will inevitably result in higher prevalence of presbyopia, attention to which should be considered, as this is an unnecessary source of visual impairment. In this study, a combination of environmental and nutritional factors were investigated, using a detailed lifestyle questionnaire and more advanced methodology, in comparison to previous studies discussed, to assess the influence on amplitude of accommodation and onset of presbyopia in a population attending optometric practice in the United Kingdom. Intraocular lenses for presbyopia have advanced, but are usually implanted as part of cataract surgery. Cataracts typically occur from 50 years onwards when presbyopia has already manifested, with patients missing out on the potential benefits of premium IOLs for many years and at the peak of their working ability. Patients are already benefiting from refractive lens exchange, replacing their hardened lens causing presbyopia, however, it is important to know when presbyopia occurs and what factors influence this as lifestyle has significantly changed since the work of Jain *et al* (1979) and Miranda (1979), with changes in diet and visual demands. A better knowledge of when individual's may become presbyopic will help with counselling on premium IOL options they might wish to consider alongside other forms of refractive correction.

5.2. Methods

Four hundred and ninety eight consecutive patients attending routine optometric practice in the West Midlands (United Kingdom), who met the inclusion/exclusion criteria and gave consent, participated in the study. They were aged between 18 years to 90 years, with an average age of 42± 23 years. Ethical approval, adhering to Declaration of Helsinki, was obtained from the Aston University ethics committee. Participants required good physical and mental health with no ocular pathology, as observed by slit-lamp biomicroscopy and ophthalmoscopy and no previous ocular surgery. All participants were English-speaking to ensure instructions and questionnaires were fully understood.

Following informed consent, refractive error was determined subjectively based on the principal of maximum plus power for best distance visual acuity to ensure the patient was fully corrected for distance vision. Pupil sizes were recorded in photopic conditions (300 lux), right eye and binocular amplitude of accommodation were then measured using the RAF near point rule (H.S Clement Clarke International, Harlow, Essex, United Kingdom) as the push-up technique is the most widely accepted method for measuring subjective amplitude of accommodation. For pre-presbyopic patients measurements were obtained whilst fully corrected for distance. However, for presbyopes a +2.00 dioptre lens addition was used required to allow for measurements to be taken within a more sensitive range on the RAF rule. Push-up and pull-down techniques were carried out three times for both monocular and binocular amplitudes of accommodation using the Snellen chart optotype on the instrument. For push-up measurements, subjects were asked to view their lowest line of acuity at 40cm as the target was slowly moved towards them. Observers were asked to report when the target became blurry and could no longer be resolved. For pull-down measurements, the optotype was positioned initially in front of the point of blur on push-up testing; the target was then slowly pulled away from the observer until it could again be resolved. The reference point at which measurements were made was the spectacle plane, located 12mm from the cornea. Additional lighting was used to illuminate optotypes to ensure high contrast at all distances (range 80 to 100cd/m^2). The same examiner carried out all measurements of accommodation for all subjects to reduce inter-examiner variability.

Minus lens measurements of accommodation were also obtained by presenting minus lenses in 0.25 dioptre steps from blur to initial clearance of a 6 metre target. The target viewed was determined as the individual's lowest line of distance visual acuity on a computerised logMAR chart. These two methods were used to allow comparison with previous studies on the development of presbyopia (*table A4*).

In addition, adult participants were asked to complete a lifestyle questionnaire which is not validated but has previously been used as part of age-related macular degeneration studies. Questions included dietary intake, alcohol intake, medical conditions and medication, UV exposure, iris colour and supplement intake (see appendix for questionnaire, A1).

5.3. Statistical Analysis

For statistical comparisons the amplitude of accommodation with the RAF rule was calculated as the average of push-up and push down values, in order to provide the best estimation of accommodation (Zadnik, 1997). As the RAF rule was determined as more sensitive to accommodative change with age (see chapter 6), these values were used for the correlation with lifestyle in preference to the minus lens technique. As both eyes should be affected by any of the lifestyle issues evaluated, binocular RAF rule amplitude of accommodation was considered. All data was assessed for normal distribution using the Kolmogorov-Smirnov test. Comparisons between categories were performed using analysis of covariance (ANCOVA) with age as a covariate, as it is known to be the strongest factor associated with amplitude of accommodation. Non-parametric data was analysed using Kruskal-Wallis and Mann-Whitney U tests. Linear regression modelling was used to determine which variables may influence accommodation.

5.4. Results

5.4.1. Onset of Presbyopia

All presbyopic participants were asked when they first required a reading prescription which would indicate the onset of presbyopia, as at this time a patient seeks help from a practitioner due to inability to carry out near tasks satisfactorily. The average age of onset of presbyopia, reported by the population that participated in the study was calculated as 48.9 ± 7.3 years. The average age of presbyopia onset for females was 48.2 ± 7.2 years and for males it was 49.7± 7.4 years, these results however showed no statistical difference ($p=0.11$).

Average photopic pupil size for male presbyopes was calculated as 3.19 ± 0.05mm, for females it was 3.17±0.05mm, although this showed no statistical difference ($F=0.07$, $p=0.79$).

5.4.2. Age & Gender

Binocular amplitude of accommodation with the RAF rule, calculated as the mean of binocular push-up and pull-down values and minus lens technique amplitudes were compared. Both techniques show decrease in amplitude with age (*Figure 5.1*).

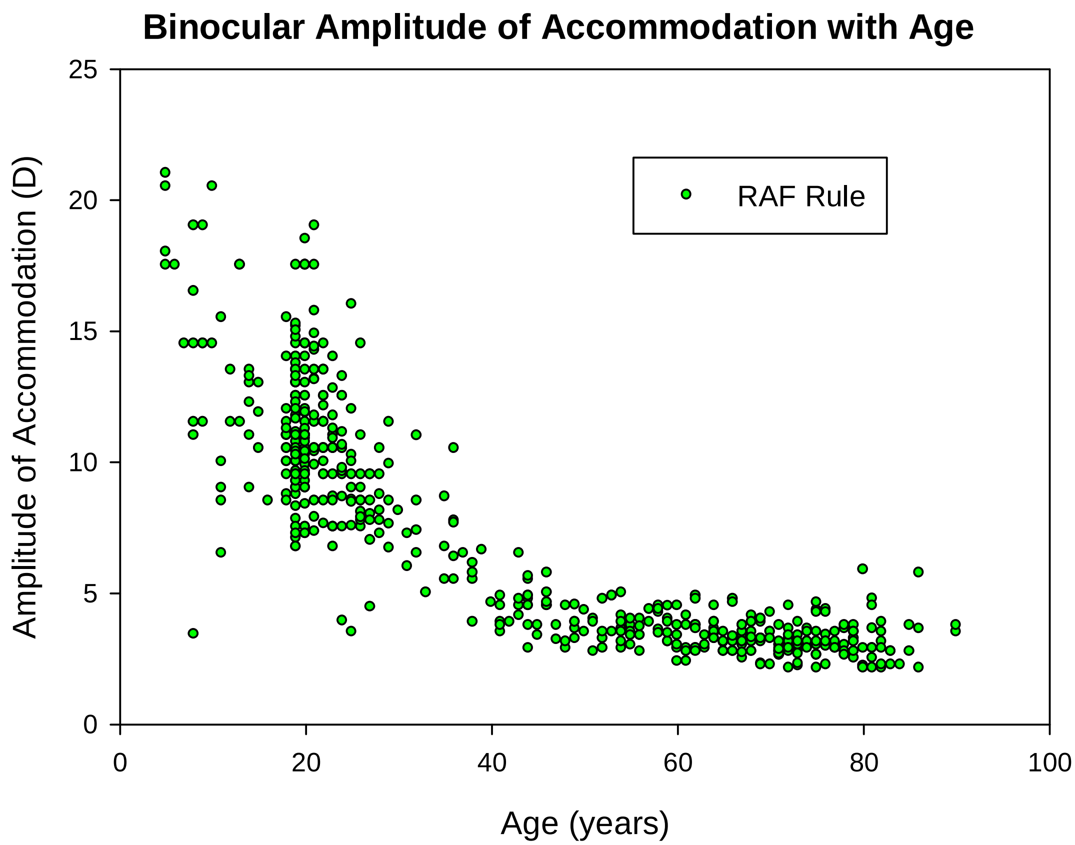


Figure 5.1: *Comparison of binocular amplitude of accommodation with RAF rule (n=536)*

The relationship between age and binocular accommodation with RAF rule was investigated by performing analysis of Pearson product-moment correlation coefficient. A strong negative correlation was present between age and accommodation, where an increase in age results in a decrease in accommodation, for males; $r= -0.86$, $n=215$, ($p<0.001$) and for females; $r= -0.85$, $n=278$ ($p<0.001$).

On age-controlled comparisons of accommodation between gender, pre-presbyopic females (<45 years) showed higher average binocular amplitude of accommodation, with the RAF rule, of 10.29 ± 3.29 D compared to an average of 9.54 ± 2.77 D for pre-presbyopic males, although this was just outside statistical difference ($p=0.06$). Presbyopic males (≥ 45 years) exhibited a mean amplitude of accommodation of 3.46 ± 0.76 D compared to females with mean amplitude of 3.39 ± 1.00 D; again this was not found to be of statistical significance ($p= 0.5$, *Figure 5.2*).

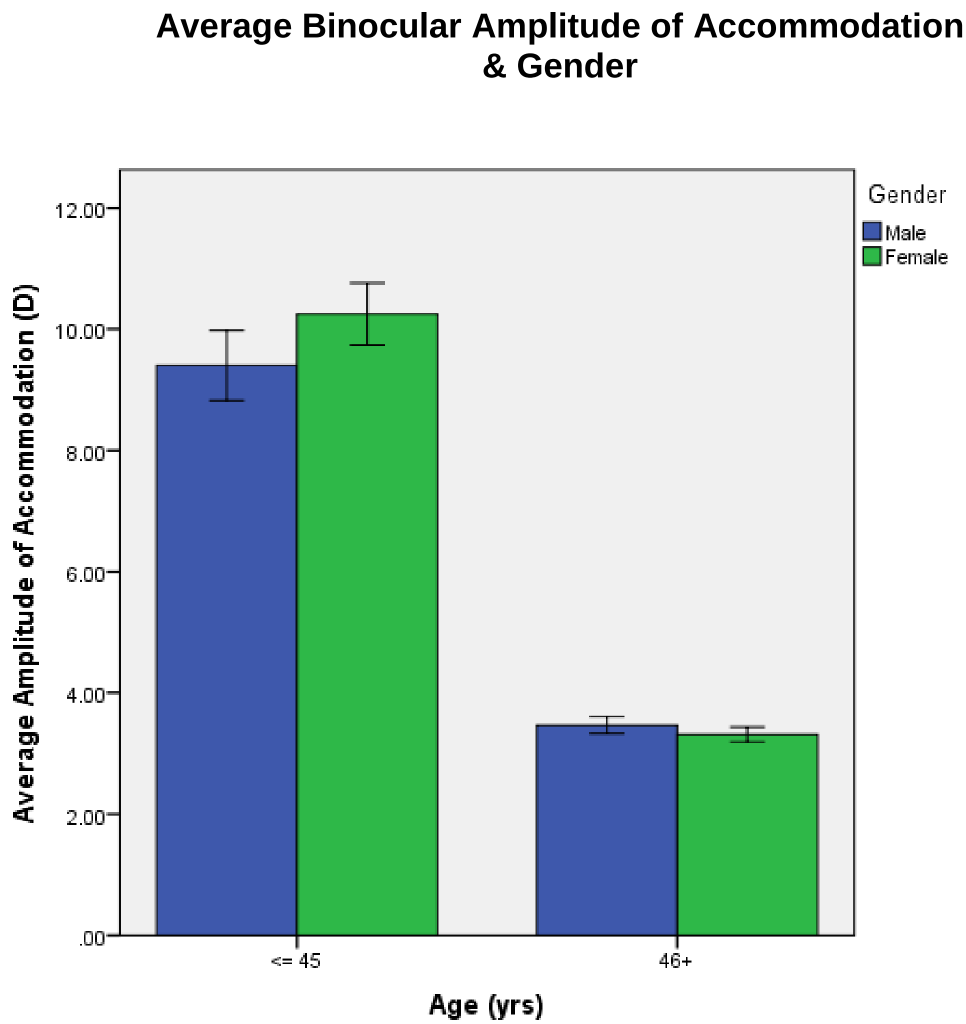


Figure 5.2: *Comparison of average binocular amplitude of accommodation between pre-presbyopic and presbyopic males (n=215) and females (n=278). Error bars = 1 S.D.*

5.4.3. Height, Weight & Body Mass Index (BMI)

For height (cm) no association with accommodation ($r= 0.06$, $n= 493$, $p= 0.202$) was found. Weight (kg) showed a very small positive association, with a Pearsons correlation coefficient of 0.11, found to be of significance ($p=0.014$, $n= 493$). However, Body Mass Index (kg/m^2) showed a significant stronger negative association with accommodation, ($r= -0.44$, $n= 493$, $p<0.001$).

5.4.4. Ethnicity

To investigate the influence of ethnicity on accommodation, comparisons weremade only between the two largest ethnic groups found from the questionnaire; British (n=103) and South Asian (n=90). A one-way between-groups analysis of covariance (ANCOVA) was conducted to compare the two major ethnic groups from results of the questionnaire and their binocular accommodation values obtained with the RAF rule; the independent variable being noted as ethnicity, the dependent variable set was accommodation and age selected as a covariate.

No significant differences were found amongst the ethnic groups ($F= 3.31$, $p= 0.07$, partial eta squared= 0.02).

5.4.5. Iris Colour

Comparisons of iris colour groups; black/dark brown, blue, brown, green, grey, hazel and light brown, were made as these were the most common categories obtained from the questionnaire. One-way between-groups analysis of covariance (ANCOVA) was conducted to compare iris colours and binocular accommodation values obtained with the RAF rule, the independent variable being noted as iris colour, the dependent variable was set as accommodation and age selected as a covariate.

Differences between iris colour whilst controlling for age were found to be significant (F= 5.96, p<0.001, partial eta squared= 0.09). 9% of the variance in accommodation, according to the analysis, can be explained by iris colour. Further post hoc comparisons with the Tukey HSD test shows black/dark brown (7.42± 0.28D, n=59), brown (5.76± 0.21D, n=85) and light brown (6.21± 0.43D, n=19) irides significantly differ from blue (5.54± 0.19D, n=108) and grey (5.29± 0.41D, n=22) irides. The darker irides gave higher values of mean accommodation in comparison to lighter irides. The three groups of brown iris colours (Black/dark brown, brown, light brown) also showed statistical differences between each other, with black/dark brown giving the greatest adjusted mean amplitude of accommodation. Green (5.28± 0.34D, n=31) and Hazel (5.72± 0.31D, n=37) showed no statistical differences with all iris colour groups.

5.4.6. Ultraviolet Light Exposure & Climate

To investigate the possible effects of ultraviolet (UV) light and climate on amplitude of accommodation, subjects were asked a number of questions; the hours spent outside per week in Spring/Summer months and Autumn/Winter months, annual exposure to strong sunlight abroad and the total number of weeks in hot climates throughout the individual's entire lifetime. Generally the hours spent outdoors in daylight were more in the Spring/Summer (24.57± 20.14 hours) period than in Autumn/Winter period (15.07± 14.14 hours, $p<0.001$). To investigate if a relationship exists between the number of hours outdoors per week in warmer and colder seasons and accommodation, partial correlation was conducted between binocular amplitude of accommodation (RAF rule) and the two sets of seasons. Again controlling for age was a requirement for this analysis.

For hours of UV exposure per week in the Autumn/Winter months, a significant but relatively small negative association was found ($r= -0.12$, $n= 491$, $p= 0.01$), suggesting that the less hours an individual spends outside in the colder seasons, the higher the amplitude of accommodation. Surprisingly, the correlation between binocular accommodation and weekly exposure to UV light in the Spring/Summer months showed only a borderline association ($r= -0.08$, $n=491$, $p=0.06$).

Participants were also asked for how many weeks of their annual holidays they were exposed to strong sunlight abroad. Partial correlation showed no significance between annual exposure to strong sunlight and amplitude of accommodation ($r = 0.01$, $n = 491$, $p=0.77$). Using the total number of weeks spent abroad in hot climate in the participant's entire lifetime obtained from the questionnaire to explore the possibility of an association between hot climate and amplitude of accommodation, partial correlation gave no significant association between time in hot climates throughout a lifetime and amplitude of accommodation ($r= 0.01$, $n=491$, $p=0.82$).

5.4.7. Ultraviolet Light Protection

Within the questionnaire, participants were asked about their UV protection and how often sunglasses were worn during times of bright sunlight. Answers were split into categories of; always, most of the time, sometimes, occasionally, very rarely and never.

A Kruskal-Wallis test was conducted and revealed a significant difference amongst the six groups ($p<0.001$, $\chi^2 = 39.76$). Never wearing sunglasses generated a lower median than all other groups except for always wearing sunglasses. Mann-Whitney tests were conducted between all groups and showed a significant difference in amplitude of accommodation between never (Md= 4.06, n=89) wearing sunglasses and four other groups; very rarely ($p<0.001$, Md= 8.12, n= 57), occasionally ($p=0.03$, Md= 7.58, n= 44), sometimes ($p<0.001$, Md= 7.94, n= 64) and most of the time ($p=0.001$, Md= 8.50, n= 71). Never wearing sunglasses and always wearing sunglasses in bright conditions, however, showed no statistical difference ($p=0.87$, Md= 3.50, n= 83).

5.4.8. Diet & Nutrition

One way between groups analysis of covariance (ANCOVA) was conducted to assess the binocular amplitude of accommodation measured with the RAF rule for meat eaters (n=428), vegetarians (n=41) and partial vegetarians (n=24). No vegans were found to have participated in the study. The covariate was selected as age. However, the different categories in diet did not show any significance in the level of binocular accommodation measured (F=2.12, p= 0.12).

For more detailed information on dietary intake patients were asked how many separate servings of fruit and vegetables they consumed per week and how many eggs and oily fish were eaten per week. One cup of fruit or vegetables was defined as a serving of food. Fruit and vegetable intake per week was combined to give an overall estimate of weekly intake by summing up the separate serving scores for fruit and vegetables. Partial correlation was used to explore the relationship between the combined intake per week and binocular accommodation (RAF Rule) whilst controlling for age. No significant association was found between fruit and vegetable intake and binocular accommodation (r =0.007, n=491, p=0.88).

The recommended daily intake of fruit and vegetables is known to be 5 servings of both fruit and vegetables per day, making a weekly intake of 35 servings. To investigate if this recommendation may of benefit to accommodation levels, one way between groups analysis of covariance (ANCOVA) was conducted for weekly intake of less than 35 servings of fruit and vegetables (n=441) and 35 or more (n=52). No significant difference in accommodation was found between individuals adhering to the recommended intake and those not achieving the recommended intake ($F=0.19$, $p=0.66$, partial eta squared<0.001).

The number of eggs consumed per week and accommodation was also assessed using partial correlation, again controlling for age. Again, no association was found ($r=0.03$, $n=491$, $p=0.51$), hence suggesting the number of eggs consumed does not affect binocular accommodation. Partial correlation was again used to assess if a relationship exists between the amount of oily fish consumed per week and binocular accommodation (RAF rule). Oily fish intake per week also did not show any significant relationship on binocular amplitude of accommodation ($r=0.03$, $n=491$, $p=0.51$).

5.4.9. Alcohol Consumption

To assess the effects of alcohol consumption adult participants were asked if they consumed alcohol and if so how many units were consumed per week. One way between groups analysis of covariance was used to compare the binocular accommodation (RAF rule) between participants that drink alcohol (n=263) and participants that do not drink alcohol (n=230), with the covariate set as age. The results of the ANCOVA show some significance in the differences of amplitude of accommodation between the alcohol drinkers and non-alcohol drinkers (F=9.91, p=0.002, partial eta squared= 0.02). The mean accommodation was higher for those that do not drink alcohol (6.81 ±0.13 D) in comparison to those that do (6.26 ± 0.12 D).

In order to investigate how much alcohol is required to affect accommodation, partial correlation analysis on binocular accommodation and the units of alcohol consumed per week, whilst controlling for the effect of age. No correlation was found as the value was just outside significance (r= -0.11, n= 263, p=0.07), suggesting that for participants in the current study, the quantity of alcohol consumption did not affect levels of accommodation.

5.4.10. Smoking

All adult participants were asked if they smoked cigarettes, subjects were then split into two groups of smokers and non-smokers. Binocular accommodation values measured with the RAF rule were compared for both presbyopic and pre-presbyopic smokers and non-smokers. Comparisons of average accommodation with the RAF rule within pre-presbyopes (<45 years) show significantly lower average accommodation for smokers (n=23) compared to non-smokers (n= 236, p< 0.001). The reverse is shown in presbyopic subjects (≥ 45 years) where smokers (n=38) exhibit a significant and slightly higher mean amplitude of accommodation with the RAF rule compared to non-smokers (n=196, p<0.001, *Table 5.1, Figure 5.3*).

	Pre-Presbyopes (<45 yrs)	**Presbyopes (≥ 45 yrs)**
Non-smokers	10.25 ± 2.98D	3.32 ± 0.68D
Smokers	7.21 ± 3.51D	3.75 ± 0.79D

Table 5.1: *Average amplitude of accommodation (dioptres, D) measured using RAF rule for pre-presbyopes and presbyopes*

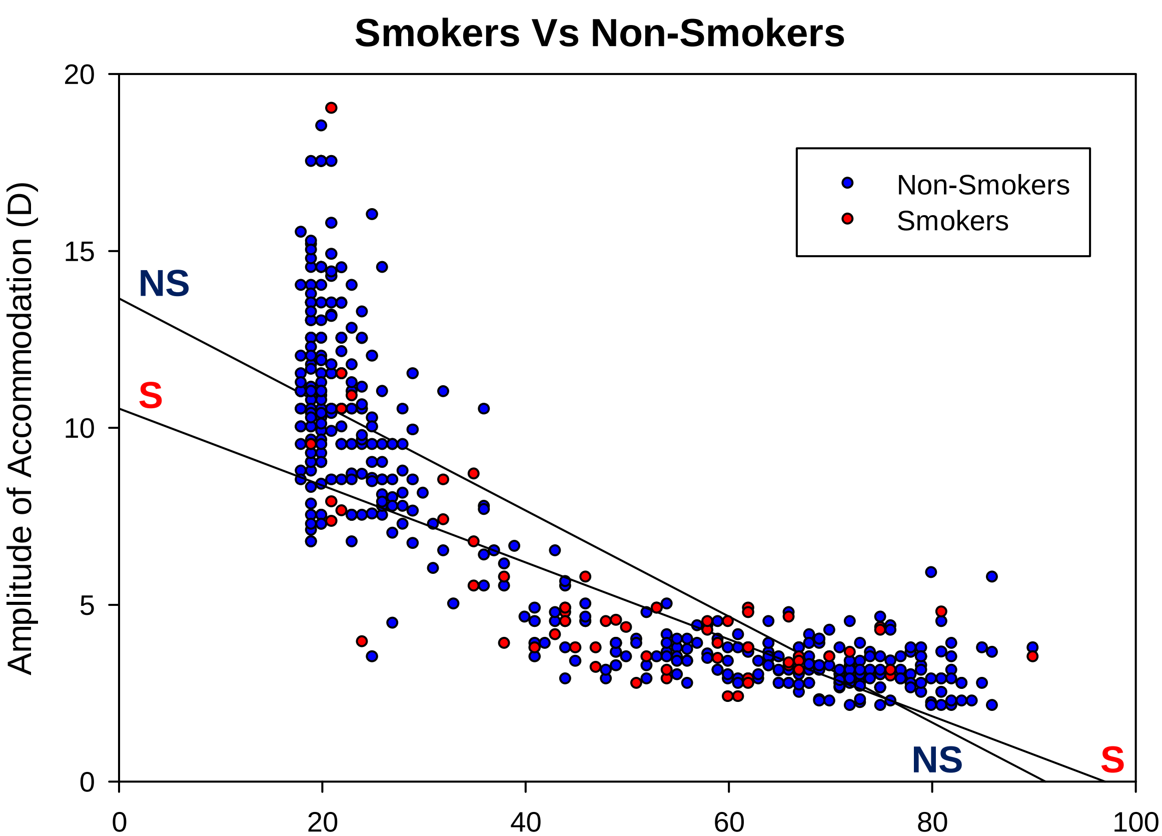


Figure 5.3: *Comparisons of smokers and non-smokers*

One way between groups analysis of covariance (ANCOVA) with age set as the covariate also confirmed an overall difference between smokers and non-smokers ($F=13.36$, $p<0.001$, partial eta squared 0.3). Smokers showed reduced mean amplitude of accommodation (5.93± 0.27D, n=61) in comparison to non-smokers (6.98D± 0.10D, n=432).

To determine if there is any variation amongst the quantity of cigarettes smoked, one way analysis of covariance (ANCOVA) was also carried out within the smoker group. Comparisons of those smoking less than 100 cigarettes per week and 100 or more cigarettes per week, whilst controlling for age, showed a significant difference ($F= 6.72$, $p= 0.01$, partial eta squared= 0.1). Smokers that smoke 100 or more cigarettes per week seem to possess greater amplitude of accommodation once age has been controlled for, with adjusted means of 10.50 ± 0.35D and 12.14D ± 0.49D for smoking less than 100 cigarettes (n=39) and 100 or more (n=22), respectively.

5.4.11. Vitamin Supplement Intake

As part of the questionnaire, patients were asked if they used vitamin supplements, such as multivitamins, as part of their diet in the last ten years. Comparisons of the binocular accommodation (with RAF rule) between individuals taking vitamin supplements once a day for ten years (n= 125) and those not taking supplements (n= 368) were made using one way between groups analysis of covariance (ANCOVA), with age as a covariate. Intake of vitamin supplements showed no significant affect on amplitude of accommodation (F= 1.92, p= 0.17, partial eta squared= 0.004).

5.4.12. Diabetes

One way between groups analysis of covariance was used to explore the differences in binocular accommodation with the RAF rule between diabetic patients (n= 89) and non-diabetic patients (n= 404), age was selected as a covariate. No significant difference was found between the two groups, (F= 2.56, p= 0.11, partial eta squared= 0.005), but there were only 89 diabetics in the population examined.

5.4.13. Hair Dye

Comparisons between groups that have used hair dye in the last ten years (n= 138) and those that have not (n=355) were carried out using a one way between groups ANCOVA, with age as a covariate. A significant difference was found between the two groups (F= 5.51, p=0.02), with the group not using hair dye showing a greater mean of binocular accommodation with the RAF rule (6.99 ±0.11 D) then the group using hair dye (6.49 ± 0.18D). Suggesting hair dye use may have some involvement in accommodation levels.

5.4.14. VDU & Mobile Phone Use

To investigate how more recent visually demanding technology may affect accommodation, subjects were asked if they used a laptop or PC and mobile phones. To assess if the amplitude of accommodation differs between users of VDUs and non-users a one way between groups analysis of covariance (ANCOVA) was performed, with age set a covariate. Interestingly, the analysis showed a significant difference amongst the two groups ($F= 5.77$, $p= 0.02$), suggesting that using a VDU may have some influence on accommodation levels. However it must be noted although age was controlled in this analysis, 74% of the users were pre-presbyopes (<40 years of age). The mean RAF amplitude of accommodation, controlled for age, was slightly greater amongst those that do not use VDUs (6.96± 0.21D, n= 173) compared to those using VDUs (6.27± 0.13D, n= 320). Partial correlation was then used to investigate if the number of hours daily using a VDU also influenced amplitude of accommodation, again the effect of age was controlled for. No significant correlation was obtained between number of hours daily on VDUs ($r = 0.01$, $n= 320$, $p=0.31$) and RAF binocular accommodation, suggesting the amount of time spent working on computers does not affect accommodation, but using or not using does.

For mobile phone use, one way between groups analysis of covariance was also used to explore the differences in accommodation between those using mobile phones and those that do not. Again age was selected as the covariate. The difference between users and non-users of mobile phones significantly differed in binocular accommodation values with RAF rule ($F= 10.32$, $p=0.001$, partial eta squared=0.021). Again the majority of mobile phone users were pre-presbyopes (62%, <40 years). With age adjusted, non-users of mobile phones show greater mean binocular amplitude of accommodation (7.18± 0.22D, n= 110) than mobile users (6.33± 0.11D, n= 383).

5.4.15. Near Work

Patients were asked how many hours per day they spend on near tasks such as reading. To assess if the amount of time carrying out near tasks and levels of accommodation are associated, partial correlation analysis was used. No significant correlation was found between the number of hours spent on near tasks per day and accommodation ($r= -0.05$, $n= 493$, $p= 0.31$) with the RAF rule.

5.4.16. Near Working Distance

Parametric comparisons were made to determine if the preferred near working distance of an individual influences the onset of presbyopia or rather the requirement for reading spectacles.

A significant positive correlation between near working distance and presbyopia onset exists ($r = 0.17$, $n = 236$, $p = 0.01$), therefore as the preferred working distance increases, the later an individual will require reading spectacles. However, the correlation is small suggesting that near working distance is a small factor influencing presbyopia in addition to others.

5.4.17. Modelling of Continuous Variables

To form a model of predicting presbyopia onset and level of accommodation, continuous variables including age, gender, weight, height, BMI, alcohol units consumed were investigated. The effect of smoking, diabetes, UV exposure, diet, use of hair dye, mobile phones and VDU usage were also investigated controlling for the variables found to affect the model.

For stepwise linear regression modelling, age, height, weight, BMI, weekly fruit and vegetable intake, alcohol units, hours spent outdoors in autumn/winter and spring/summer, weeks spent abroad in strong sunlight per year, total time spent in hot climates through lifetime, hours spent on near tasks daily and reading distance were all entered as variables. The model shows only age, weight, units of alcohol units consumed per week, hours spent outdoors in autumn/winter and reading distance to have some affect on accommodation, excluding the other variables that were entered. The model obtained was given as follows;

Accommodation= 16.876 + (Age – 0.135) + (weight -0.023) + (reading distance -0.053) + (alcohol units – 0.023) + (hours autumn/winter – 0.013)

The final R^2 value was 74.6%, hence the majority of the variation in binocular accommodation with the RAF rule can be explained by the model shown above, with the additional variables excluding age adding 2.3% to the variation in accommodation.

Categorical regression in which the remaining non-continuous variables were entered showed smoking, diet type, alcohol consumption, sunglass wear, vitamin intake and diabetes to account for a small variation in accommodation. The R^2 value calculated as 13.7% indicating a small influence on accommodation yielded by the categorical model. Use of VDU shows the greatest measure of relative importance (0.42) and is thus fundamental to the regression model. The relative importance for smoking (0.06), diet type (0.12), alcohol (0.14), sunglass wear (0.10), vitamin intake (0.007), diabetes (0.08) and mobile phone use (0.06) were all much lower in comparison. Tolerance values for smoking, diet type, alcohol, sunglass wear, vitamin intake and diabetes all have found to be near 1, hence cannot be predicted well from one another and show less bearing on the regression model. VDU and mobile phone use show tolerance values of 0.61 and 0.63 respectively, although relative importance of mobile phone use was only 0.06.

5.5. Discussion

With both techniques of measurement a definite decrease in amplitude of accommodation was evident with age. The average age of patient reported onset of presbyopia (nearly 49 years) which was similar for males and females was considerably higher than previously reported by other researchers (please refer to appendix, *table A4*). The difference may be explained by improvements in healthcare and considerable changes in diet and general lifestyle and seem to concur with when the objective data asymptotes.

The onset of presbyopia between males and females did not differ significantly, despite females showing slightly earlier development, similar to Hickenbotham *et al* (2012, *in press*). There is a general agreement that females tend to develop presbyopia earlier than males (Nirmalan *et al*., 2006; Millidot *et al*., 1989; Koretz *et al*., 1989; Kragha 1986; Miranda 1979; Carnevali and Southaphanh 2005; Morny 1995). Although hormonal differences have been suggested as possible reasons, recent work by Hickenbotham *et al* (2012, *in press*) have demonstrated the differences are attributed to preferred near working distances and differences in hobbies requiring near vision rather than physiological variations and focusing ability. In addition, length of arms, occupation, and lighting tasks may also influence the requirement for reading spectacles. Therefore, the measurement of amplitude of accommodation alone does not provide sufficient information on presbyopia as one must consider the visual requirements of the patient

(Hickenbotham *et al.,* 2012, *in press*). Consideration of depth of focus, high order aberrations and pupil size in future research is also recommended to determine any differences between males and females. Near working distance amongst women has already been determined (Millidot and Millidot 1989) and seems the most likely factor in the earlier development of presbyopia as the physical stature of women is much smaller than men. Women over 40 years also show a tendency towards hyperopic refractive errors (Kempen *et al.,* 2004) which may exacerbate near vision symptoms leading to an earlier prescription for reading spectacles.

No previous work has considered height, weight or body mass index (BMI) as possible contributors to levels of accommodation and onset of presbyopia, even though they may relate to arm length and eye size. Within the current results no association was found between height and accommodation. Weight and BMI, however, showed a small relationship with accommodation. Weight was positively associated with accommodation indicating as weight increases amplitude of accommodation may also increase, though this was only a small relationship it was of enough significance to be included in regression modeling. Conversely, BMI showed a negative relationship, suggesting as BMI increases the amplitude of accommodation will decrease, the magnitude of this relationship was far greater than that of weight but unusually was not included in regression modeling. Height and weight alone, clearly do not show a vast bearing on accommodation, however when combined to give an overall score such as body mass index, a relationship with accommodation may be observed.

Ethnicity has long been recognized as a considerable contributing factor to the age of onset of presbyopia and bears a significant effect on accommodation levels. Caucasians have been reported to possess greater amplitudes of accommodation in comparison to other ethnic groups (Covell, 1950, Rambo and Sangal, 1960), although it is not always to differentiate this from environmental conditions at some point in the subjects' history. Covell (1950) reported a 5 to 10 year early onset of presbyopia amongst black migrants with a very rapid decrease in accommodation when compared to white Panamanians, this was distinguished by examining the near additions prescribed to both ethnic groups. Hofstetter (1968, 1949) had also reported a higher addition for near work was prescribed to black patients in comparison to Caucasians in the order of ~0.50 dioptres. In addition, Olurin (1973) stated an early onset of presbyopia in native Nigerians, where 48% aged 35 to 40 years old require near additions. Further research by Ong (1984), as previously mentioned, discovered a particularly earlier onset of presbyopia, below the age of 35 years, in Southeast Asian refugees. These studies on presbyopia and accommodation have reported differences between ethnic groups originating from different countries. No retrospective studies have investigated differences between ethnic groups within in the same country or region. In the present investigation all participants were UK residents.

Similar to Carnevali and Southaphanh (2005), investigating presbyopia in Hispanic and non- Hispanic groups and Hunter *et al* (1997), no statistically significant differences were found amongst ethnic groups within the current study. The lack of significance between results is not unexpected, as all ethnic groups were residents of the United Kingdom and have hence been subjected to the same climate and general lifestyle. Such a finding suggests rather than ethnic origin influencing accommodation levels, climate and geographical location may be more valuable factors for consideration.

Age-related lenticular changes, such as cataracts have been associated with darker irides in numerous studies (Leske *et al*., 2002; McCarty *et al*., 1999; Cumming *et al.,* 2000, Delcourt *et al.,* 2000). The general notion being darker irides absorb more heat energy and transfer this to the crystalline lens inducing thermal damage and aging (Langley *et al.,* 1960), which in turn increases the risk of opacities and hence may even play a role in reducing amplitude of accommodation. It is also suggested that iris melanin may produce free radicals through UV exposure which damage the lens (Mason *et al.,* 1960). However, as the present study has found greater binocular amplitudes with brown irides compared to blue irides, it could be postulated that darker irides absorb more UV radiation protecting the crystalline lens from UV damage. A similar finding was cited in a study investigating iris pigment and UV radiation in rats, where cataracts developed more in non-pigmented rats than the pigmented species (Löfgren *et al.,* 2012). The authors also suggested darker irides may absorb more sunlight hence provide better protection, in addition melanin may provide protection against damage (Hill *et al.,* 1997) due to proclaimed antioxidant properties (Löfgren *et al.,* 2012). Previous findings of association with opacities and dark irides may be influenced by the geographical locations in which research was carried out, the investigations tended to be in regions of hot climate with high levels of sunlight where darker irides are most prevalent. Furthermore, these regions consist of lower socio-economical status and poorer nutrition which also may have affect the rate of aging.

Ultraviolet light (UV) is defined as three sets of wavelengths; UVA of wavelengths 315-400nm, UVB of wavelengths 280-315nm and UVC with the shortest wavelengths of 100-280nm. The shorter the wavelength the more energy is carried and hence increase the severity of any damage caused. In the young eye, the cornea absorbs any UVC penetrating the atmosphere and the lens absorbs any UVB traversing the cornea, though aging processes this absorption may increase to include UVA (Bergmanson and Söderberg, 1995). Chronic UV exposure can significantly deteriorate ocular health, external effects include development of pterygia and piguecula on the conjunctiva and photokeratitis, with reports of pleomorphism and polymegathism as possible results of UV damage. Internally, damage through macular degeneration and cataracts may develop. It is therefore assumed that UV light may induce aging of the crystalline lens (Stevens and Bergmanson, 1989).

The lens is also very sensitive to temperature and lifelong exposure can accelerate ageing by affecting metabolic processes of lens epithelium. As discussed previously there is strong evidence suggesting a link between presbyopia and hot climates as well as with increased exposure to UV light, whereby presbyopia develops much earlier in regions of warmer climates with high levels of sunlight (Stevens and Bergmanson, 1989). Also Miranda (1979) has suggested an earlier onset of presbyopia with lower latitudes.

UV light of 290-400nm causes considerable damage to the crystalline lens and prolonged exposure to 290-400nm throughout life has been associated with accumulation of chromophores and increase in the insoluble proteins within lens fibres (Lerman, 1980). Various studies have described processes by which UV light may cause damage to induce aging of the lens, which could explain the earlier onset of presbyopia closer to the equator. Light exposure may induce an inflammatory response within the eye, which leads to the release of reactive oxygen species that damage tissues, photoxidation may also lead to production of reactive oxygen species by pigments within the eye (Roberts, 2011). As the lens is made up of dead proteins, which accumulate through life, any damage to the proteins also accumulates as no processes exist to remove damaged cells (Andley, 2008; Young, 1992). UVB induced damage has also been linked to increased calcium levels; this is believed to activate a substance called calpain which damages crystallin proteins (Hightower and McCreedy, 1997). Damage to the lens by UV radiation can occur in as little as 24-48 hours, with experimentation showing swelling of epithelial cells, granules within cytoplasm and formation of peripheral wall cells within 48-72 hours of exposure (Pitts *et al.,* 1977). Changes within the anterior epithelium have also been noted particularly within pupil area, although the damage appeared to reverse after ten days (Duke-Elder 1926, 1954). Tryptophan, found in ϒ- crystalline, when irradiated with UV light produces chromatic photoproducts that bind to the lens proteins and change their colour and make them insoluble (Zigman *et al.,* 1972). Furthermore, mice experiments by Zigman *et al*., (1974) and Zigman and Vaughan (1974) have shown epithelial cells lose their differentiation ability to form fibre cells 35 weeks following chronic exposure, cataract development soon manifested after 50 weeks.

Environmental temperature, as shown by Miranda (1979), presents a strong negative correlation with onset of presbyopia. Schwartz (1965) showed the temperature in rabbit lenses to be 8℉ higher with an environmental temperature of 75℉ compared to 50℃. As metabolic rates increase to almost double with increased tissue temperature, it is likely that aging will occur sooner. In the current study, no significance was found in accommodation results and how much time an individual spent abroad in hot and sunny climates annually or throughout their lifetime. However, the number of hours spent outdoors in winter and autumn showed a positive correlation but time spent outdoors in summer and spring was just outside statistical significance. Individuals wearing sunglasses in bright conditions also showed higher accommodation values than if sunglasses were never worn, suggesting protection around the eyes in bright conditions will reduce the level of UV damage to the crystalline lens.

Time spent outdoor in autumn and winter may have shown more significance on accommodation results as it is unlikely that any UV protection is worn around the eyes during the colder months. Also, with the low-lying sun during these seasons one may be exposed to more UV light than anticipated. The finding of reduced accommodation amongst constant wearers of sunglasses in bright light could be explained by the disadvantages of sunglasses. Wearing sunglasses may inactivate the mechanism of squinting, which attempts to provide some protection against excessive light exposure, additionally, pupil dilation may be stimulated by dark glasses allowing more access to light coming from around the frame of sunglasses (Corneo 2011; Deaver *et al.,* 1996; Sliney 2001). Perhaps for these reasons, the group wearing sunglasses ‘most of the time’ presented the highest levels of accommodation compared to all other categories, as this would not completely inhibit defense mechanisms. However, the importance of eye protection against UV radiation must be expressed to patients and the general public despite these claimed disadvantages of sunglasses. Sunglasses should be of wraparound style to provide the best protection. Persons wearing fulltime refractive correction should be advised on UV coated lenses and contact lens wearers should be encouraged to opt for lenses providing UV filters. UV protection in children must also be stressed as the development of presbyopia is the result of life-long metabolic processes of the crystalline lens and the retina is not fully protected from UV until adulthood, hence earlier protection may help prevent signs of early aging.

The role of diet in various age-related processes and disease has become of growing interest among researchers. Increased fruit and vegetable intake is recommended with age as normal rates of antioxidant production are reduced with advancing age (Jacques *et al.,* 2001; Lyle *et al.,* 1999). Through aging the crystalline lens endures photoxidative damage, oxidation of lens proteins may cause changes within the lens, eventually resulting in senile cataracts (Jacques *et al.,* 1997). Studies have shown reductions in age-related conditions such as cataracts and macular degeneration with increased intake of antioxidants such as vitamin C, E, A and carotenoids, this may be due to their protective effects against oxidation (Jacques *et al.,* 1997; Jacques *et al.,* 1994; Taylor *et al.,* 1993). Results from questioning participants on fruit and vegetable intake, however, did not demonstrate any benefits to accommodation; multivitamin supplementation also did not show any significant effect on accommodation levels. Similarly, Taylor *et al* (2002) observed no association between antioxidant intake and cataract formation, though did report an association between low vitamin C levels with lens opacities in women below 60 years of age, the chances of which could be reduced through long-term vitamin C supplementation. Jacques *et al* (1997) recommend observing supplement intake over a ten year period as shorter time scales may fail to demonstrate any effects. Questioning on supplementation was indeed refined to intake over 10 years but results failed to indicate any effects with amplitude of accommodation. It is believed that social status may influence the quality of nutrition and diet and hence rate of presbyopia onset, as reports within developing countries have determined earlier onset. Hunter *et al* (1997) have shown social economic status does not impact presbyopia and again suggests further research into causative factors of early presbyopia.

Consumption of alcohol has been shown to result in lower amplitude of accommodation compared to no alcohol consumption. The number of units consumed did not show any significant change in binocular accommodation levels, though it should be emphasized that there may have been a bias in information from patients as to how many units were consumed. It should be noted, however, the results from minus lens measures (not presented in the results) showed a negative correlation with weekly alcohol units, where increases in number of units consumed correlated with lower amplitude of accommodation. The effects of alcohol on aging of the human body and normal functioning of processes in the body are well known. Although the effects of alcohol consumption on accommodation and presbyopia have not widely been researched, Campbell *et al* (2001) have noted lower accommodation, measured with the RAF rule, with excessive consumption particularly in young subjects. These findings were sustained a week later following a period of no alcohol consumption and therefore cannot be explained by blood alcohol levels as this period of time is sufficient for eradication of alcohol within the bloodstream. An increase in pupil size is also noted in alcoholics which may reduce depth of focus and hence reduce accommodation.

Alcohol may have an effect on lens homeostasis and has already been implicated in cataractogenesis with moderate to heavy consumption (Manson *et al*., 1994). Fatma *et al.,* have also shown cytotoxic effects of ethanol on lens epithelial cells whilst previous research has shown alterations in membrane permeability which may affect permeability of calcium (Harding, 1995, Zeng *et al.,* 1998). Additional studies have shown toxic effects of alcohol leading to loss of LEDGF protein in lens epithelial cells (Fatma *et al.,* 2004), losses of this protein are correlated with cell death due to stress. Reductions in LEDGF in cells may impair homeostasis and hence functioning of cells. Furthermore, LEDGF is a transcriptional regulator of the genes ADH and ALDH, both of which participate in detoxification of cells from ethanol toxicity. Less LEDGF may hence reduce this action making the crystalline lens more susceptible to damage through alcohol consumption (Fatma *et al.,* 2004).

Cigarette smoking has already been categorised as being cataractogenic (Cekic, 1998), hence smoking may affect amplitude of accommodation and onset of presbyopia. Smokers were found to exhibit significantly lower accommodation when compared to age-matched non-smokers, particularly in pre-presbyopes. In presbyopes, however, the opposite occurred where smokers had significantly higher amplitudes, although this was a small difference of only ~0.4 D. It has been stated that 2.6% of cataracts may be attributed to smoking (van Heyningen & Harding, 1988), the risk of which may be increased in diabetic smokers (Klein *et al.,* 1985). Numerous toxins within tobacco smoke are particularly harmful to ocular structures causing ischemic or oxidative stress (Mosad *et al.,* 2010). Oxidative stress is known to induce opacities within the lens (Balasubramanian *et al.,* 1993) but it is reasonable to assume this may initially affect accommodative ability and lead to early presbyopia. Various substances such as cadium, cyanide, thiocyanide, free radicals and aldehydes are all increased within smokers (Reznick *et al.,* 1992). Aldehydes may cause damage by attacking proteins and enzymes within the crystalline lens (Harding, 1993). Cadium levels are of particular concern, as increased amounts have been noted in cataractous lenses which increase further with the number of cigarettes smoked (Cekic 1998; Mosad *et al.,* 2010). Reports have suggested that cadium may denature lens proteins (Ramakrishnan *et al*., 1995) or affect copper metabolism, which is required for enzyme functionality (Cook & McGahan, 1986). Increased levels of copper and lead have also been noted in lenses of smoker which may be due to the activity of cadium within the lens (Cekic, 1998). Cadium has a half-life of approximately 30 years, hence is able to cause disruption within the human body for some time, possibly inducing premature aging of the lens.

Smoking is also linked to lower levels of antioxidants, such as vitamin C, E and carotenoids (Christen *et al.,* 1992; Hankinson *et al.,* 1992). These antioxidants ‘quench’ free radicals that may otherwise cause oxidation (Klein *et al.,* 1985), such substances may therefore aid the prevention of premature aging of the lens but seem to be reduced in smokers which may provide some understanding of the reduced accommodation found in the smoker group of the present study. Although cadium levels increase with increased numbers of cigarettes, no significance was found on amplitude of accommodation with the amount of cigarettes smoked. In addition, presbyope smokers showed slightly higher accommodation which could possibly be attributed to disruption or inhibition of metabolic processes in the lens epithelium that eventually cause aging.

Diabetes Mellitus has been associated with early onset of various age-related conditions (Cahill, 1979) and hence may exhibit lower amplitudes of accommodation. With age the crystalline lens of diabetic patients, when compared that of healthy subjects, is thicker and more convex in shape (Brown *et al.,* 1982; Saw *et al.,* 2007; Huggert 1953; Brown and Hungerford 1982). Cataracts also tend to occur more frequently and at an earlier age with diabetes sufferers (Bron *et al*., 1993). It is estimated that duration of diabetes has 70% more of an effect than age on the lens per year (Sparrow *et al.,* 1990; Goldmann, 1964), making it a significant factor to consider in onset of presbyopia. The increase in lens thickness is believed to be due to increases in the size of the cortex and nucleus (Sparrow *et al.,* 1990), particularly the cortex, with effect being more apparent in type I diabetics. Weimer *et al.,* (2008a) has also shown variations in the structure of the lens with diabetes compared to controls, again with greater changes in type I diabetes. The thickness of the cortex and nucleus were found significantly thicker in diabetes type I, duration of diabetes was a significant factor showing a positive relationship with thickness. Type II diabetes, however, showed less effect on the structure of the lens. Weimer *et al* (2008a) proposed two theories to explain the increase in thickness – the theory of enhanced growth and theory of lens swelling. The increase in thickness of the lens could be attributed to an increase in lens fibre production through using insulin (Reddan *et al.,* 1982, 1983). Alternatively, the lens swelling theory may provide better explanation, in which increases in thickness could be resultant of overhydration of the crystalline lens by increased influx of water, this is supported by findings of lower refractive index in type I diabetes (Weimer *et al.,* 2008b). Both Pierro *et al* (1996) and Weimer *et al* (2008a) have found no association with lens structure and metabolic control of the condition, examining metabolic control for longer periods however may show different effects. Diabetic retinopathy and photocoagulation have also shown to pose no effect on the lens (Sparrow *et al.,* 1992).

The results of the current study found no significant difference between diabetic patients and healthy individuals. Such a finding may perhaps be warranted by better control of diabetes now due to better healthcare compared to previous studies. In addition, all diabetics within the study were late-onset which, as proven by the studies discussed, show variations in lens structure to a lesser extent. Moss *et al* (1987) showed reduced amplitudes in younger diabetic patients, the results were obtained using only pull-down values. Comparisons by the authors against data presented by Duane (1925) showed a significantly lower mean accommodation, though this may have been influenced by differences in methodology. However, within the study by Moss *et al* (1987), a difference between non-diabetics and diabetics was still found and other factors including duration of diabetes, diabetic retinopathy and poor metabolic control were also implicated as affecting accommodation. In addition, hypoxia may contribute to lower levels of accommodation by disruption of circulation (Moss *et al.,* 1993). Oxidative stress may be increased in diabetes (Bron *et al*., 1993), this may lead to earlier age-related changes as oxidation of lens membrane can increase its permeability (Duncan *et al.,* 1991). Other findings include more light scattering in diabetic lenses (Weiss *et al.,* 1982) which is more marked with retinopathy and photocoagulation. A combination of all the structural variations described in diabetic lenses may thus all contribute to perceived lower levels of amplitude of accommodation.

Toxins such as hair dye have been reported by Jain *et al* (1982) as a possible agent in earlier onset of presbyopia. Users of hair dye within the present study appeared to have significantly lower binocular accommodation than individuals that had never used hair dye. Jain *et al* (1982) observed 4% of patients with early onset of presbyopia were longstanding users of hair dye; similarly an earlier study by the same authors recorded early presbyopia onset in 7% of hair dye users with 89% showing some form of lenticular changes. The exact effects of hair dye on the crystalline lens have not been extensively researched; however, it is believed paraphenylene diamine, found in hair dye, may pose toxic effects on the metabolic reactions within crystalline lens leading to an earlier onset of presbyopia (Jain *et al.,* 1979, 1982). Further research into chemicals within hair dye affecting the crystalline lens and accommodation may thus be a worthwhile area of research.

With recent advances in technology, the use of mobile phones and VDUs are rising, resulting in different demands on the visual system. This study demonstrated that users of computers and mobile phones both show significantly reduced levels of binocular accommodation in comparison to non-users of both devices. Similar findings have been found in other studies (Tyrell and Leibowitz, 1990; Gur et al., 1994). This may link to various reports of asthenopic symptoms and fatigue through prolonged and regular use of VDUs (Bergqvist 1989; Smith *et al.,* 1984). The exact mechanism as to how VDU use may impact the visual system is unclear, a suggestion by Jaschinski-Kruza (1988) of overload on the convergence system which in turn affects accommodation and causes fatigue may provide some explanation, as in their study a further working distance of 100cm was preferred to 50cm by VDU users. These collective findings suggest that prolonged and regular use of VDUs may contribute to the earlier onsets on presbyopia, although, interestingly in this study it was found that the number of hours using a VDU daily did not significantly affect the levels of accommodation. Mobile phone use has not been previously investigated, making this the first study to assess its bearing on accommodation. As mobile communication (SMS messaging, emails) is effectively another form of near task, excessive convergence fatiguing the visual system may too explain the difference in accommodation levels of users and non-users.

No association was observed between the number of hours an individual carries out near tasks daily and the binocular amplitude of accommodation. This is not surprising as the accommodative system has been shown to be very resistant to fatigue (Wolffsohn *et al.,* 2011). As expected, a significant positive correlation was found for working distance and onset of presbyopia, therefore as an individual's preferred working distance increases the age of presbyopia onset increases. The onset of presbyopia is often defined as the point at which one cannot sustain focus satisfactory for near tasks, prescription of reading spectacles bring the focus point closer to the cornea allowing a comfortable working distance. Those with closer preferred working distances hence will require reading spectacles far earlier to maintain comfortable vision, whereas those working at greater distances can persevere for longer before finding difficulty with near tasks.

5.6. Conclusion

It is clear that in addition to age, presbyopia is influenced by many environmental factors; this study has shown significant variations in accommodation with alcohol consumption, smoking, UV exposure and even weight. Understanding the factors which influence the onset of presbyopia will enable practitioners in the future to advise patients how their lifestyles may influence their individual rate of progression and onset of presbyopia. Presbyopia is a widespread and inevitable visual deficit and although cannot be cured, many advanced IOLs are available which aim to provide spectacle independence in presbyopes. Better education of patients as to the causes of presbyopia and how it may be effectively managed including the option of clear lens extraction is hence warranted. Using questionnaires, however, to gather information from patients presents as a significant limitation within the current study, as for example there may have been biased answers for questions regarding diet and alcohol consumption. Bias in information would therefore influence the results of the investigation.

One of the major limitations of this and all subjective accommodation studies is the variability in the push-up/down techniques due to the changing visual angle of the target, pupil size changes and luminance variations. Hence the next chapter described and evaluates new technology developed in conjunction with engineers to attempt to overcome some of these limitations.

CHAPTER 6

Validity and Repeatability of a Digital Accommodometer

6.1. Introduction

Accommodation is the ability of the crystalline lens to change the dioptric power of the eye to clearly focus on objects closer than infinity (Glasser, 2008). With age this ability reduces resulting in near objects becoming blurry and indistinguishable; this progressive reduction is a result of age rather than actual ageing of the eye, where clarity at near can no longer be sustained to satisfy an individual's needs (Gilmartin, 1995). Presbyopia is usually first noticed around the age of 40 years and continues gradually until no accommodation remains (Hamasaki *et al*,. 1956). Amplitude of accommodation may be described as the dioptric distance between the near and far points of accommodation.

Accommodation can be measured with subjective or objective techniques. Such measurements may be used to investigate asthenopic symptoms associated with near tasks or to evaluate the amplitude of accommodation gained following presbyopia-correcting surgical procedures such as following implantation of accommodating intraocular lenses. Objective measures of the optical change in the power of the eye can be made using autorefractors or aberrometers (Mallen *et al.,* 2001; Wolffsohn *et al.,* 2004; Win-Hall and Glasser 2008; Wold *et al.,* 2003). They need to be open-field to not induce proximal accommodation (Rosenfield and Ciuffreda 1991; Wolffsohn *et al.,* 2002) and to allow presentation of a target that optimally stimulates accommodation (such as a high contrast Maltese Cross), often within a Badal optical system to negate changes in target resolution and lighting with changes in working distance (Atchison *et al.,* 1994). Objective measures are good at assessing real accommodation without the confounds of pupil size, optical aberrations and perceptual factors which result in a depth of focus range before blur is noticed by an individual. However, it is also important to understand how well an individual performs in the real world where both real and pseudo-accommodation interact with subjective accommodation measures. It is particularly useful to measure subjective accommodation when assessing presbyopia-correcting surgery and implantation of multifocal or accommodating IOLs as objective measures do not provide evidence of accommodation to support the functional near vision achieved (Wold *et al.,* 2003).

In clinical practice subjective amplitude of accommodation is most commonly determined using push-up and push-down techniques such as using the Royal Air Force (RAF) rule (HS Clement Clarke International, Harlow, Essex, U.K.). The procedure involves advancing an optotype of fixed size until the patient reports sustained blurring of the target and then moving the optotype away from the observer until clear. When a subject's amplitude is higher than can be measured on the scale of the RAF rule, as in younger patients, additional negative lenses are required to extend the test range and to make the test more sensitive as dioptre changes reduce in physical distance as accommodation increases. For older subjects positive lenses are required due to low amplitude of accommodation being off the end of the scale.

The RAF rule, however, does possess limitations for example artificially higher values of amplitude of accommodation have been reported with this using the push-up technique compared to objectively measured accommodation (Rosenfield *et al.,* 1996; Ostrin and Glasser 2004). Factors contributing to this include the eye's depth of focus include pupil size and ocular aberrations (Ostrin and Glasser 2004; Atchison *et al.,* 1994) as well as the subject's tolerance to blur (Ostrin and Glasser 2004; Rosenfield and Cohen 1996). The use of a constant target size may also lead to unreliable results, as with reducing distances, the angular subtense of the optotype increases leading to poor blur detection and over-estimation of the amplitude of accommodation particularly with higher amplitudes (Ostrin and Glasser 2004; Atchison *et al.,* 1994; Rosenfield and Cohen, 1995). To account for this patients can be instructed to change fixation to a smaller target as the current target blurs, however if the target is too large, accommodation may be over-estimated. Also if the target is too small to resolve accommodation may not be stimulated. It is suggested that targets should subtend 5 minutes of arc at 20cm for measurements of subjects under 30 years of age (Berens *et al*., 1950) whilst others suggest a target size of 6/6-6/9 (London, 1991; Grosvenor, 1989; Carlson, 1990). Constant lighting may also be an issue with the RAF rule as this will affect the effective contrast of the target and hence accommodative demand, in addition to pupil size which influences the depth of focus of the eye. The RAF rule is generally operated by the examiner, hence there may be a small delay in reacting to when the patient reports blurring of the target, which may vary between examiners; to overcome this, patients may be asked to take control by moving the target themselves. The speed at which the target approaches the observer is often difficult to keep consistent between examiners or patients and may also affect the stimulation of accommodation.

Donders (1864) was the first to investigate accommodation and mapped out values of binocular amplitude of accommodation for various ages which have since been used as the standards for comparison of other similar investigations. However, flaws within the experimental technique may have resulted in these findings being inaccurate. Donders' experiment employed the push-up technique using thin vertical wires as targets and measured accommodation using the nodal point of the eye, located 7mm behind the cornea. Subjects were assumed to be emmetropic or near emmetropia. As Donders used the push-up technique to define his values of accommodation amplitudes there may be some over-estimation in the results hence these values required re-assessment. Duane (1909, 1912) later revised Donders findings in an attempt to provide more accurate measures of accommodation. The push-up test was again used with test targets of single, thin vertical black lines with the near point taken as the first point of reported blur from the spectacle plane, located approximately 13mm in front of the cornea. Emmetropia was ensured in all subjects through use of cycloplegia and distance correction. Comparisons of amplitude of accommodation curves obtained by Duane (1909) and Donders (1864) show overall data findings by Duane report lower amplitudes of accommodation. Duane also noted higher binocular amplitude of accommodation than monocular, the difference between which reduced with increasing age. The differences between the findings of the two authors are likely to be resultant of the methodology employed, highlighting the reduced accuracy of Donders technique (Hofstetter, 1944). Although Duane offered more reasonable values for amplitude of accommodation the push-up test was again used, in addition to targets which may not appropriately stimulate accommodation.

A more refined technique would need to include a method to control or take into account depth of focus which may prove challenging due to functioning of the near triad response on such testing procedures. Stigmatoscopy, as used by Hamasaki *et al* (1956), may be a solution to minimise depth of focus. Hamasaki *et al* (1956) compared push-up and stigmatoscopy accommodation and found push-up amplitudes generally coincided with that of Donders and Duane. In addition, the measures of stigmatoscopy gave much lower estimates of amplitude of accommodation in comparison to push-up values, with a mean difference of 1.75D. Push-up measurements declined up to 50-52 years and remained fairly constant up to 60 years. Conversely, beyond 52 years stigmatoscopy demonstrated absolute presbyopia. Depth of focus hence presents as a significant limitation in subjective push-up measurement of accommodation.

There are very few reports investigating the repeatability of subjective measurements of accommodation. Brozek *et al* (1948) and Rosenfield and Cohen (1996) investigated the push-up, pull-down and minus lens techniques at near reporting that although the techniques showed significant difference between one another. Rosenfield and Cohen (1996) reported similar repeatability with all three measurement techniques as no statistical differences were found upon repeated readings (p=0.95), with standard deviations of 0.73D, 0.71D and 0.73D reported for the push-up, pull-down and minus lens methods, respectively. Antona *et al* (2009) investigated intra-examiner repeatability with the same three techniques and suggested where multiple techniques are being used for validity and repeatability purposes the same examiner should perform all measurements, but found the minus lens method to be most repeatable technique with the least mean difference of -0.08D and 95% agreement interval of ±2.52D. Generally, with the RAF rule three measurements are still taken with the instrument although there is no standardised procedure for its use, as numerous measures should always be made with subjective methods (Duane, 1909).

Taking all these factors into consideration a new and more accurate subjective method of measuring amplitude of accommodation would be beneficial, for example in assessing accommodation following presbyopia-correcting surgery, assessing near vision gained with premium IOLs and investigating asthenopic symptoms associated with near tasks. A new hand-held electronic device has thus been constructed to measure the amplitude of accommodation which is back illuminated to a constant luminance and detects its distance from the patient, allowing it to maintain a target of constant visual angle. The current study aims to validate the accuracy and repeatability of this digital accommodometer against the traditional RAF rule and the minus lens to clear technique in a wide age range of patients attending optometric practice.

6.2. Methods

One-hundred and twenty four consecutive subjects between ages of 19 and 85 years (average 52.8 ±20.2 years) attending optometric practice were included in this study, following informed consent. The study was approved by the University Ethics Committee and followed the tenets of the Declaration of Helsinki. Exclusion criteria included any form of ocular pathology, ocular abnormality such as binocular vision problems and any form of ocular surgery. All subjects participating in the investigation were required to speak English to ensure the procedure was fully understood, as this can affect blur detection and hence amplitude measurements (Rosenfield *et al.,* 1996, Ostrin and Glasser 2004). A corrected distance visual acuity of at least 0.0 logMAR (6/6) was required in all subjects, with near vision acuity of N5 or better at 40 centimetres. Ocular health was checked with a slit-lamp biomicroscope and ophthalmoscope. The study consisted of a single visit where patients were refracted using the maximum plus prescription without reducing optimum visual acuity technique and fully corrected before accommodation measurements were taken with the digital accommodometer and RAF rule in random order. Refractive error, age and gender of patients were also recorded.

The digital accommodometer (*Figure 6.1*) used was a hand-held device developed at Aston University displaying a target letter ‘E’ on a small 4.5cm x 6cm Liquid Crystal Display (LCD) screen of resolution 800 x 600 pixels, luminance 150cd/m^2 and contrast set at 90%. It has two ultrasonic sensors which detect the working distance to the patient and automatically adjusts the size of the target to maintain the same visual subtence as is determined as the smallest size of letter the patient can just read with the device initially held at their arm’s length.

The RAF rule (*Figures 6.2, 6.3*) consists of a 50cm four-sided rod, with markings of distance in centimeters from the subject, dioptric values of these distances, a guide for age and level of convergence to aid the determination of poor amplitude of accommodation or convergence. A small moveable target attached to the rod consists of a rotating cube which displays four optotypes. For the purposes of the current study the small Snellen chart optotype was used which ranges from N12 to N4 acuity.

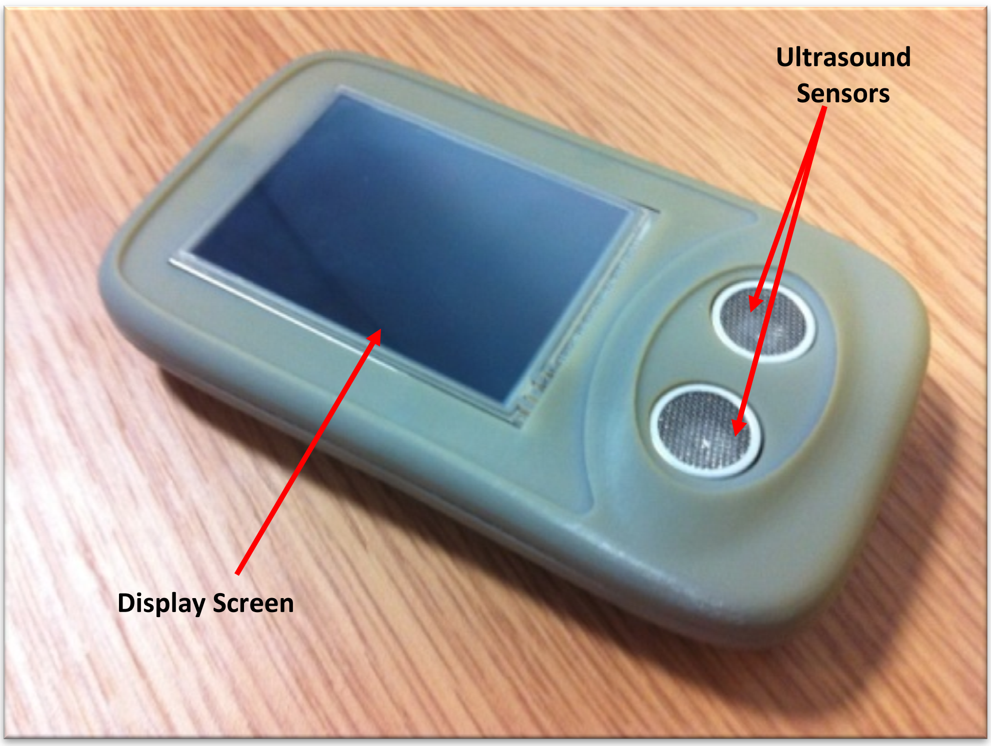


Figure 6.1: *Electronic Accommodometer*

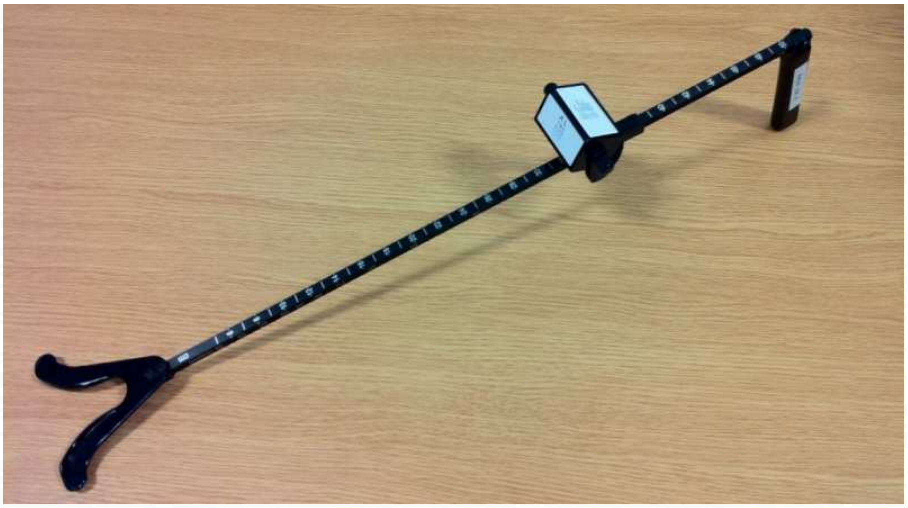


Figure 6.2: *RAF (Royal Air Force) rule; 50cm rod with four optotypes.*

Figure 6.3: *Snellen optoype used for measurement of amplitude of accommodation*

Amplitudes of accommodation were measured with the digital accommodometer (*Figures 6.4, 6.5)* binocularly both from far to near and near to far to represent push-up and pull-down amplitudes respectively. First, the accommodometer was held at arm's length and the size of the E target adjusted until it was just visible to set the target visual angle for the tests. To perform far to near measurements, subjects were asked to hold the accommodometer at arm's length, focus on the letter 'E' and slowly bring the device closer until the target began to blur, the accommodometer then needed to be held static at that distance for 5 seconds, after which the final working distance (the average of 5 readings, one each second while the device is held at the minimal clear distance) was presented on the screen and were recorded by the examiner. For near to far measurements the accommodometer was held by subjects as close as possible to the nose and pulled back until the target appeared clear. Again the same results were recorded as above. Both procedures were repeated three times to assess intra-session repeatability with a time interval of 2 minutes between each measurement.

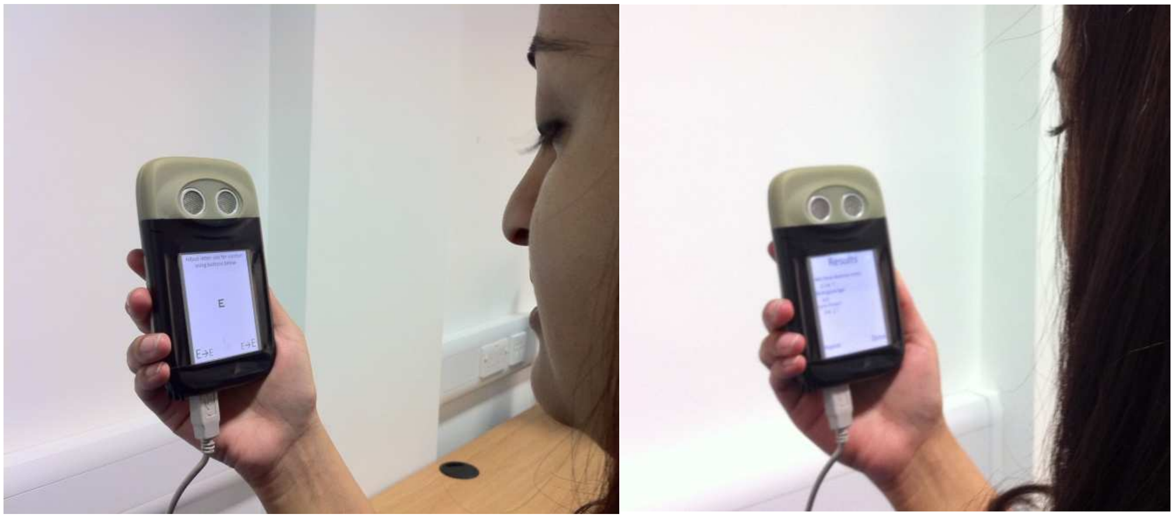


Figure 6.4: *Use of the electronic accommodometer*

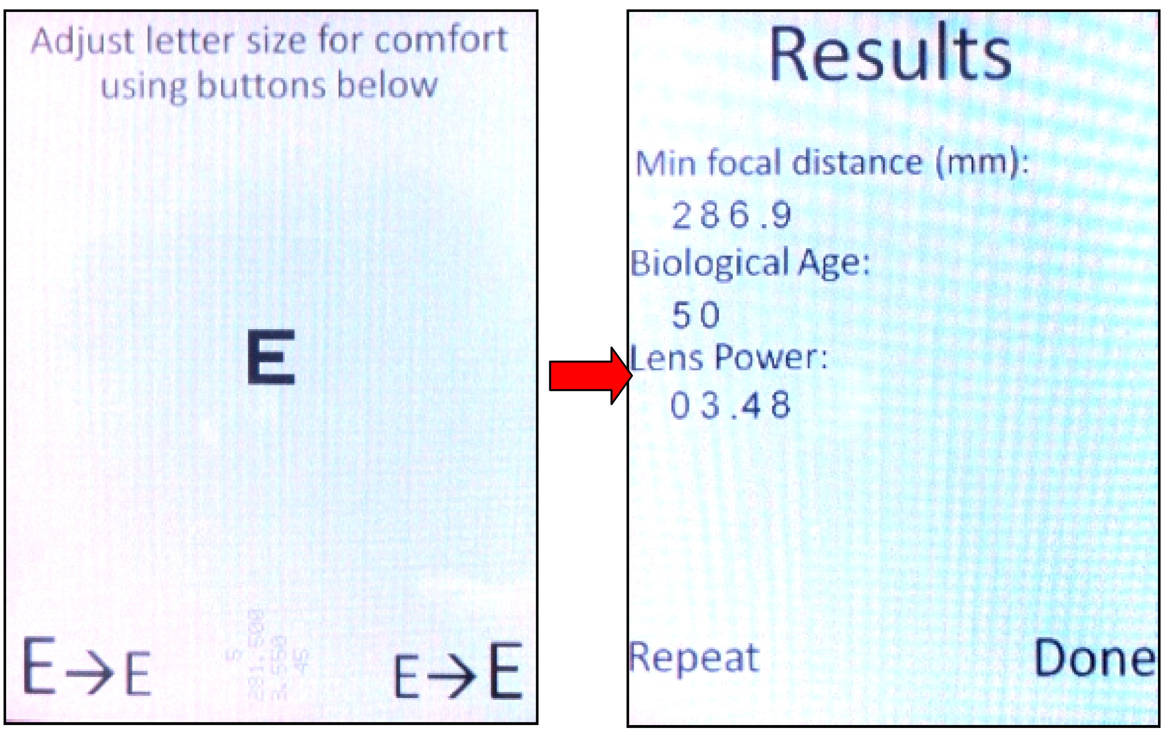


Figure 6.5: *LCD screen displaying target optotype (letter E), followed by results display screen*

For push-up measurements with the RAF rule, the rod was placed on the subject's cheeks and they were asked to view their lowest line of acuity on the small chart optotype. The target was moved at a slow constant speed from the end of the rod towards the patient until blur was first reported. The patient was then asked if the target could be made clear again if so, the target was brought closer until blur was reported. The distance at which the patient reported sustained blur was recorded. The target was then moved away from the subject and the pull-down amplitude recorded as the distance at which the target first appeared clear. Both techniques were performed three times and the spectacle plane was used as the reference point.

A third technique was also performed to measure subjective accommodation using optical rather than distance induced blur (Langenbucher *et al.,* 2003a,b; Gupta *et al.,* 2008). Subjects, wearing their distance correction were asked to view a logMAR chart 6 meters away and to view their lowest line of acuity. High minus trial lenses appropriate for the patient's age were then introduced to blur their line of best visual acuity and powers were reduced in 0.50D steps until this line again became clear. By using this lens-to-clear technique a subject's ability to accommodate over lenses could be recorded, hence giving a value for amplitude of accommodation. The highest minus lens through which the letters on the line of best acuity was correctly identified was recorded; letters on the line of best acuity were randomized on each lens presentation to avoid patients memorizing the characters. All three techniques were carried out by the same examiner in random sequence.

6.3. Statistical Analysis

Data was tested for normality using the Kolmogorov-Smirnov test and Analysis of Variance applied to parametric data. Bland-Altman analysis comparing the difference between the instruments compared to the mean was conducted plotting the results, the mean and the 95% confidence interval (Bland and Altman 1986).

6.4. Results

All three measurement techniques clearly illustrated the decrease in amplitude of accommodation with age, as shown by *figure 6.6* ($p < 0.001$). The decrease in accommodation with each measurement method for pre-presbyopes (<45 years) and presbyopes (≥45 years) are given in *table 6.1*. The accommodometer and RAF rule gave a similar reduction in accommodation with the pre-presbyopic group (<45 years) whilst the minus to lens technique estimated much less in comparison. Accommodation reduction in the presbyopes (≥45 years) was much less, as expected, compared to the reduction with pre-presbyopes. All three methods showed differences, the RAF gave the greatest reduction in accommodation followed by the minus lens technique with the accommodometer estimating the least decrease in presbyopes.

Measurement Method	Accommodative Decrease <45 years (D)	Accommodative Decrease ≥45 years (D)
Accommodometer	-0.30	-0.009
RAF Rule	-0.29	-0.05
Minus Lens to Clear	-0.21	-0.02

Table 6.1: *Decrease in accommodation for pre-presbyopes and presbyopes*

Analysis of variance (ANOVA) showed a significant difference between the three measurement techniques ($F= 341.498$, $p<0.0001$). Comparisons of the accommodometer measures and RAF rule measures showed no significant difference ($p = 0.75$) and this held for pre-presbyopes (<45 years, $p = 0.81$) and presbyopes (≥45 years $p = 0.84$). However there was a significant lower estimation of amplitude measurements with the lens to clear method in comparison with the accommodometer and the RAF rule ($p < 0.0001$).

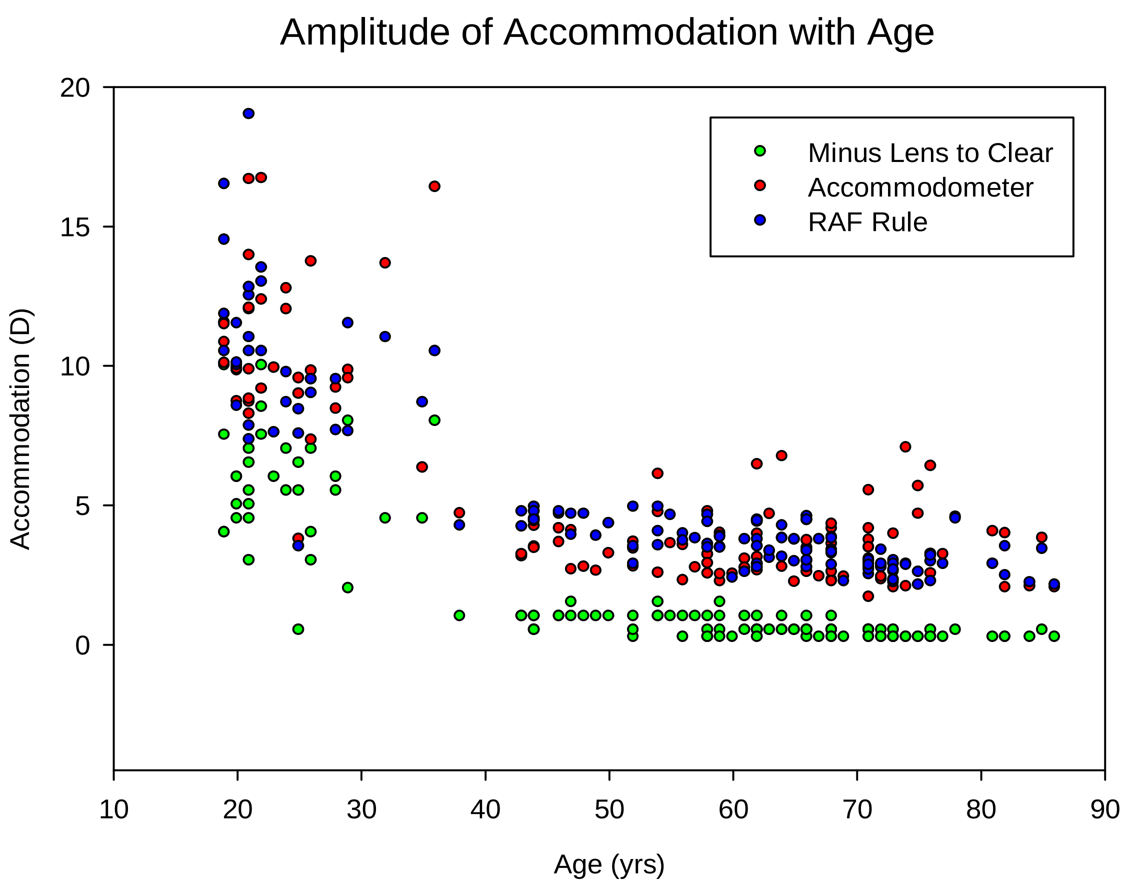


Figure 6.6: *Reduction in amplitude of accommodation (in dioptres) with RAF rule, Accommodometer and Lens to Clear technique. (n=124)*

Bland-Altman comparison of the RAF rule and accommodometer (*Figure 6.7*) showed that on average the two techniques (push-up and push-down) did indeed provide similar amplitudes of accommodation, shown as minimum focal length ($p=0.75$), however the difference between the push-up and pull-down techniques was greater with the accommodometer. The mean difference for the accommodometer was calculated as -43mm with 95% agreement interval of ± 162mm. The RAF rule gave a mean difference of -34mm with 95% agreement interval of ± 54.5mm.

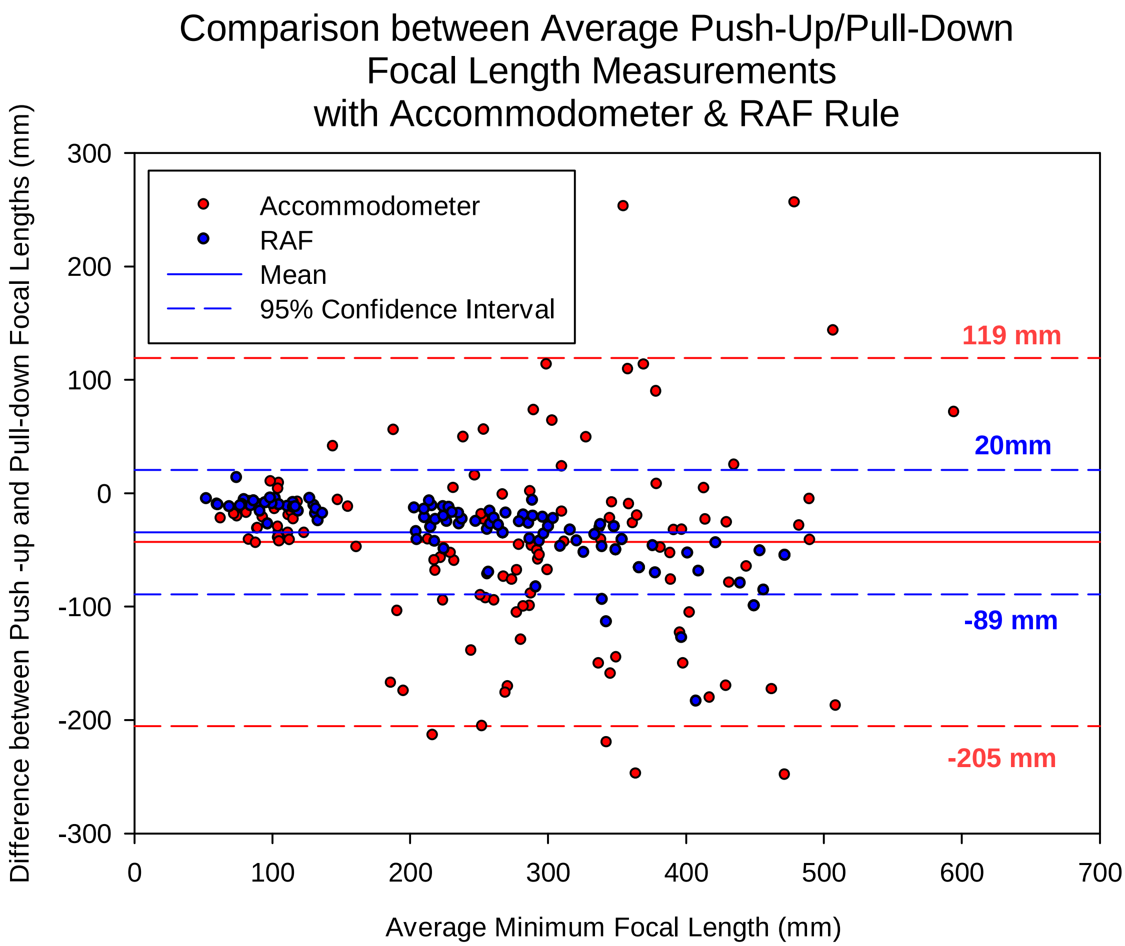


Figure 6.7: *A Bland-Altman Comparison of average minimum focal length with RAF rule and accommodometer.*

Figure 6.8 shows separate comparisons of push-up and pull-down focal lengths measured with both the digital accommodometer and the RAF rule. Mean difference for the push-up values were found to be 9mm whilst pull-down showed a greater mean difference of 18mm. The 95% confidence limits were also greater with the pull-down values at ±195mm compared to ±177mm with push-up values. No significant difference was found between these averaged results (p=0.06).

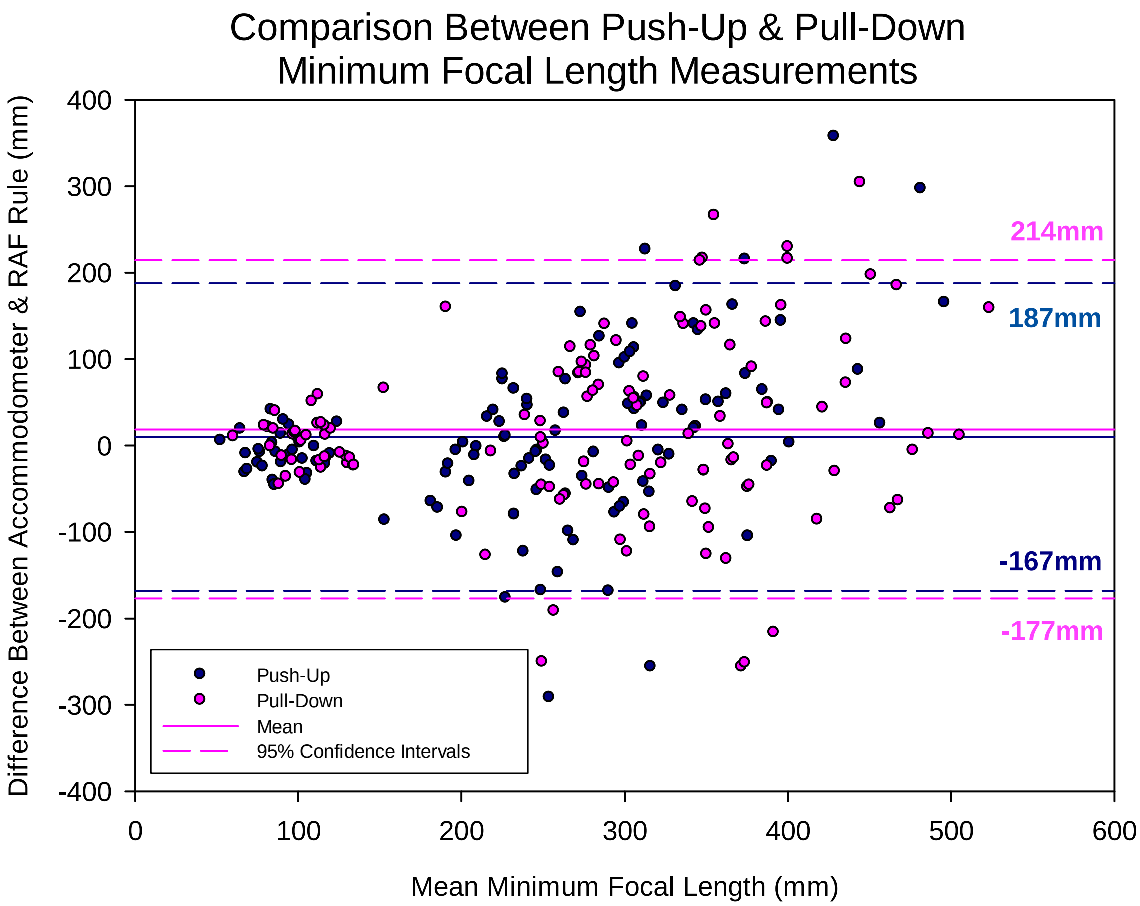


Figure 6.8: *A Bland-Altman comparison of push-up and pull-down measurement techniques*

On further analysis of push-up values with the digital accommodometer and RAF rule mean differences were found as 244± 130mm and 234± 100mm respectively, with 95% confidence limits of ±256mm with the accommodometer and ±234mm with the RAF rule, these differences however were insignificant ($p=0.22$). For pull-down measurements the mean differences were higher; calculated as 287±134mm for the accommodometer and 268±119mm for the RAF rule with 95% confidence limits of identical values of ±286mm and ±268mm and were calculated as just within significance ($p=0.05$). The mean difference and confidence intervals were higher with pull-down measurements overall in comparison to that of push-up values ($p<0.001$).

Bland- Altman plots for repeatability of the RAF rule and accommodometer (*Figure 6.9*) show acceptable repeatability for both measurement techniques which again were similar in magnitude and variability (-1.4 ± 27.5mm for accommodometer; -4.1 ± 29.0mm for RAF rule; $p = 0.09$). The plot shows there is no change in repeatability as focal length changes.

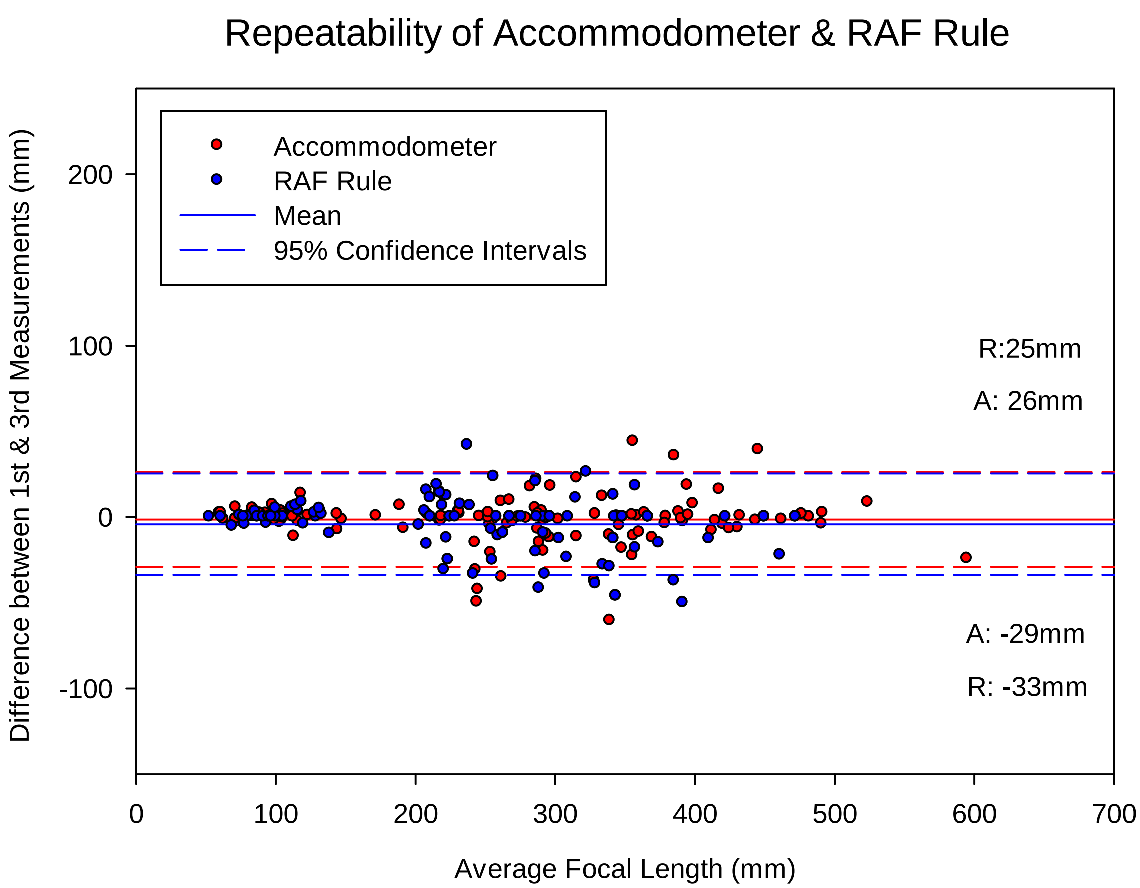


Figure 6.9: *Comparison of repeatability with RAF rule and accommodometer*.

6.5. Discussion

On analysis of the results, the accommodometer has shown the expected decrease in amplitude of accommodation and an increase in minimum focal length with increasing age up to 45 years of age; following this little or no accommodation remains and the minimum focal length measured for individuals is achieved by their depth of focus. There was no overall systematic difference between the digital accommodometer and RAF rule measurements, however the lens to clear technique was significantly different compared to both devices. The lens to clear technique is a distance task in which blur is induced by lenses. Such blurring with lenses may vary when measured subjectively as there is no standardisation in conducting this procedure (Wold *et al.,* 2003). At distance the pupil size is relatively fixed, unlike with near accommodation tasks where the near triad of responses take place to aid focusing of close objects. However, due to the minification effects of minus lenses, pupil miosis and hence the near triad of response are indeed stimulated therefore this aspect is unlikely to provide a full explanation as to why this technique differed to the accommodometer and RAF rule. Differences in target size with the minus lens technique and RAF rule may lend an explanation to differences in the results yielded. With the minus lens to clear method the target size is fixed whereas with the RAF this varies as the target brought closer to the observer leading to increased angular subtense with the RAF rule (Gupta *et al.,* 2008). Increased stimulation of proximal accommodation (depth of focus) with the RAF rule in particular may have also contributed to the differences in measurements (Gupta *et al.,* 2008). Furthermore, with the minus lens technique the target was changed on each lens presentation whereas the same target was presented with both the RAF rule and accommodometer, which may have influenced the results. Familiarity of the target may have lead to measures of greater amplitude of accommodation with the accommodometer and RAF rule as subjects will find the target easier to recognise even through blurring, whereas with the minus lens method subjects may have lacked confidence in recognising the letters correctly. However, with the push-up and pull-down techniques which require continuous presentation and movement of a target, it is difficult to keep changing optotypes although this could be done at set or random time intervals with the accommodometer screen.

The digital accommodometer, did present some variability in results. The accommodometer is required to be held at a 90 degree angle to the patient's forehead (as shown in *Figure 6.10*).

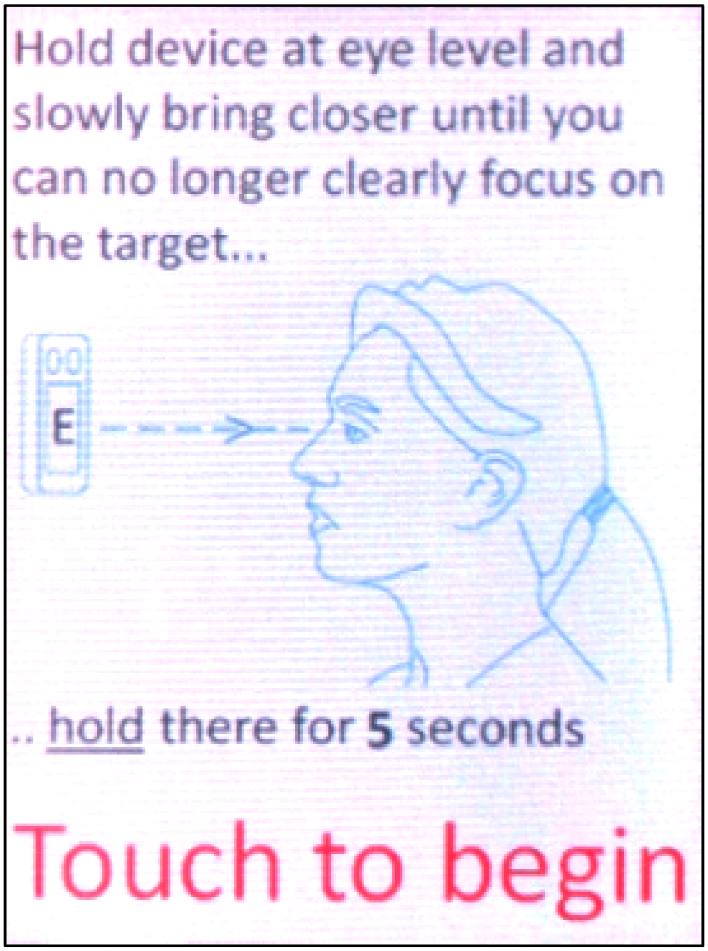


Figure 6.10:

Instructions as seen on digital accommodometer prior to taking measurements of accommodation

The accommodometer can then detect the distance between the device and patient’s forehead. However tilting of the device during the 5 second processing period may have led to other facial features such as the nose being detected instead, leading to an incorrectly estimated focal length and hence measurement of amplitude of accommodation. In addition to detecting other facial features the device may have detected lenses from spectacles (Ide *et al.,* 2012) as patients were fully distance corrected for measurement purposes. The shape profile of these lenses may have distorted the signal received by the ultrasonic sensors. The forehead also does not necessarily correlate to the position of the eyes, for example some individuals may present with deeper inset eyes. Such aspects may lead to shorter distance detection and over-estimation of accommodation.

Furthermore, the accommodometer testing procedure was patient controlled whereas the RAF rule was examiner controlled. Patient-controlled push-up tests have previously shown to yield higher results than if examiner-controlled (Fitch, 1971). To overcome this, the accommodometer testing could also have been advanced and moved away by the examiner.

Although the accommodometer is a digital device, it is still in effect a subjective method of measuring accommodation and hence shares some similar limitations as other subjective measurement techniques. For example the understanding of 'blur' varies between each individual (Wold *et al.,* 2003) with some reporting blurring when the target first begins to distort and others waiting until completely indistinguishable. To avoid this confusion all subjects were informed to stop when the target *first* became blurry and could not be made clear with effort for push-up tests and *first* became clear for pull-down testing.

Push-up testing may cause over-estimation in any subjective method (Antona *et al.,* 2009); it has been known for some time that, although commonly used in practice, the push-up test reads higher amplitudes (Fitch, 1971; Hokoda *et al.,* 1982; Wold *et al.,* 2003) reported to be between 1.50-2.50 dioptres (Rosenfield and Gilmartin; 1990, Atchison *et al.,* 1994; Rosenfield and Cohen, 1995). It is stated that such errors do not pose any clinically significant complications for young subjects, however, for those approaching early presbyopia it may lead to an insufficient correction being prescribed for near tasks (Antona *et al.,* 2009). In addition it may lead to inaccurate estimations of how much accommodation is gained following surgical procedures aiming to restore accommodation. Pull-down measurements tend to estimate lower dioptric values in comparison to push-up methods as the end-points differ. The pull-down technique begins from blurred vision, where the patient is unaware of the character they are viewing up until it is clearly identifiable, hence it may take longer until the subject is certain. With the push-up technique the target is clearly distinguishable and can still be identified whilst blurry leading to a higher reading (Antona *et al.,* 2009). Our results support this as minimum focal length was significantly greater with the pull-down technique with both the accommodometer and RAF rule hence providing lower dioptric values of accommodation. Moreover, with fixed target sizes, it is expected that the push-up technique will overestimate the amplitude of accommodation, as the angular subtense of the target will increase and induce proximal accommodation, the effect being more pronounced in younger subjects with higher levels of accommodation. For this very reason the accommodometer was designed to provide an automatically adjustable target which would subtend the same angle throughout the measurement procedure.

The contrast of the target can also affect the measurement of the amplitude of accommodation (Johnson, 1976; Tucker and Charman, 1986; Heath, 1956). The contrast of the accommodometer is 90% but this may vary with reflection of lighting, within the test area, off the LCD screen. Additional lighting was not required with the accommodometer as it provided sufficient luminance by back illumination. However results suggest that neither illumination nor constant target size has caused any consistent changes in the measurement of accommodation as observed by comparison of the accommodometer compared to the RAF rule data.

It has been suggested that the lens to clear technique might be a more appropriate measure of accommodative ability (Wold *et al.,* 2003). However the push-up and pull-down techniques may provide more useful measurements of accommodation as the 'near point of clear vision can be identified' unlike with minus lens techniques (Atchison *et al.,* 1994); also the minus lens technique is considered more variable if measured subjectively (Wold *et al.,* 2003). Furthermore push-up techniques are considered as more natural methods of measurements.

A recent paper by Ide *et al* (2012) has also investigated the use of a device similar to the Aston accommodometer in having ultrasonic sensors to detect the working distance objectively, but this measurement did not affect the target size, the target was not back illuminated and the range of measurement was only 20-50cm. Surprisingly, despite this a difference was found in measurements compared to an subjective near point measurement device.

6.6. Conclusion

In conclusion, despite some limitations with the sensors of the digital accommodometer and failure to demonstrate advantages in measurement with constant target subtense and illumination, the repeatability of both the RAF rule and accommodometer were acceptable and equivalent which suggests the new measurement technique is good, although re-working of the design is required. As a result a Smartphone version is currently being developed which should be a more compact device and overcome the variability issue as the distance between the sensors and observer is less, allowing better alignment with the subject's forehead (*Figure 6.11*).

Figure 6.11: *Prototype Smartphone Accommodometer*

The digital accommodometer although variable, has shown good demonstration of the increase in minimum focal length and profile of amplitude of accommodation with age. It has the potential to be a useful alternative to the RAF rule being more portable and maintaining the illumination and visual subtense of the target. The development of a Smartphone version of this device may offer better assessment in the near focus obtained with accommodating and multifocal IOLs.

In addition to demand for better near vision there is a growing demand for improved intermediate vision with multifocal and accommodating IOLs. Diffractive multifocal designs incorporating optics which allow three foci have been developed. The forthcoming chapter presents the evaluation of the visual performance of such a design using modern assessment techniques.

CHAPTER 7

Visual Outcomes & Subjective Experience Following Bilateral implantation of a New Trifocal Intraocular Lens

7.1. Introduction

In recent years, there have been many advances in cataract surgery procedures. Traditionally, cataract extraction involves implantation of a monofocal intraocular lens (IOL) providing adequate distance vision but the requirement of spectacles for near vision. Due to an increasingly ageing population and changes in lifestyle, the demand for spectacle independence following cataract surgery has led to the development of accommodating and multifocal IOLs.

Multifocal IOLs were first introduced in the 1990s and are now becoming more popular with new improved designs continually being developed. The two main designs of multifocal technology include refractive and diffractive optics, both of which produce simultaneous images of distant and near objects. As described in Chapter one, refractive multifocal IOLs consist of rings of different refractive powers for near and distance correction whilst diffractive IOLs use the Huygens-Fresnel principal where the IOL acts as a diffraction grating. Of the two designs it has been reported diffractive multifocal IOLs show better visual performance (Maxwell *et al*., 2009; Gatinel *et al.,* 2011).

Multifocal IOLs, although they attempt to provide spectacle independence, do not provide adequate vision for intermediate distances for many patients (Bucci 2006; Alfonso *et al.,* 2007; Petermeier *et al.,* 2007; Goes *et al.,* 2008) with reports of reduction in visual acuity within the intermediate range (Voskresenskaya *et al.,* 2010). Since the introduction of computers and boost in mobile technology in the last decade there has been a significant increase in VDU usage by the elderly population and hence demand for better intermediate vision. In 2006 it was reported the percentage of 50-65 year olds using computers doubled (Voskresenskaya *et al.,* 2010). Such a limitation would require use of spectacles solely for this working distance, hence it is suggested that multifocal IOLs are better referred to as 'bifocal' IOLs in order to avoid high expectation of intermediate vision (Voskresenskaya *et al.,* 2010).

Examples of investigations noting decreases in intermediate visual acuity include that of Hütz *et al* (2008) with the ReSTOR multifocal IOL where an average reduction down to 20/40 at distances of 40 to 80cm was reported. Blaylock *et al* (2006) also reported a decrease in intermediate visual acuity from 40 to70cm of 20/30 to 20/44 with multifocals, however, only 25% of patients reported significantly severe problems whilst 75% occasionally or never found any difficulty.

Hayashi *et al* (2009) reported a significant decrease in intermediate vision with IOLs with a +4.00D addition for near in comparison to +3.00D multifocal lenses, although the near acuity with +3.00D lenses was less than that of the +4.00D. Diffractive multifocal IOLs in particular show worse intermediate vision (Alfonso *et al.,* 2007; Blaylock *et al.,* 2006; Pepose *et al.,* 2007; Hütz *et al.,* 2008).

Visual acuity for intermediate distances may vary between individuals due to the photopic and mesopic pupil sizes. Alfonso *et al* (2007) noted those requiring intermediate correction had pupil diameters of 4-4.5mm on average in photopic condition and 6-6.5mm in mesopic conditions. They found vision with the ReSTOR multifocal deteriorated from 40 to 70cm but only 4% of subjects required spectacles for intermediate work.

Other reported limitations of multifocal intraocular lenses include haloes, glare and reduced contrast sensitivity particularly in mesopic conditions (Steinert, 2000; Richter-Mueksch *et al.,* 2002; Awwad *et al.,* 2008). Photic phenomena are reported to be 3.5 times more prevalent in multifocals than monofocal lenses (Leyland & Pringle 2006). In a study conducted by Woodward *et al* (2009) 7% of eyes required explantation to resolve the visual complications induced by the multifocal lens used.

As incident light is divided and shared amongst two foci in multifocal IOLs, overlapping of the focused and out of focus images reduces contrast sensitivity resulting in poor image quality. Poor contrast sensitivity tends to be more pronounced at lower spatial frequencies (Arens *et al.,* 1999; Vaquero-Ruano *et al.,* 1998; Steinert 2000) although there are some claims of worse contrast sensitivity at higher spatial frequencies also (Alfonso *et al.,* 2009; Montés-Micö *et al.,* 2004). Montes-Mico *et al* (2001) highlighted this compromise of contrast sensitivity at low spatial frequencies and suggested it is due to light scatter whilst that at higher spatial frequencies, the effect is mainly attributed to defocus and optical aberrations. Despite the reported reductions, photopic contrast sensitivity, although reduced in comparison to monofocal IOLs, is still found to be within the normal limits (Hayashi *et al*., 2009; Montés-Micó *et al*., 2004). Studies have also indicated an improvement of contrast sensitivity 3-6 months following implantation (Montes-Mico *et al*., 2003).

Glare is another well known phenomenon to occur with multifocal IOLs, particularly with refractive designs. It was reported 21.3% of patients implanted with ReSTOR IOL complained of glare in comparison to just 7.5% of those implanted with monofocal IOLs (Chiam *et al.,* 2006). In a survey carried out by Mamalis *et al* (2003) it was reported one of the main reasons for explanting a multifocal IOL was disability glare in addition to incorrect IOL power and IOL dislocation, as well as being the most common complaint in a study conducted by Blaylock *et al* (2006). Disability glare has been described as light which spreads over at least 1°

(Hofmann *et al.,* 2009), but is more likely to vary with individual's tolerance and environmental conditions. The size of haloes tends to be greater in patients over 70 years as light scatter from ocular structures such as; the cornea, increases with age which adds to the effect of multifocals (Dick *et al.,* 1999). Hofmann *et al* (2009) investigated retinal straylight with monofocal and multifocal IOLs and reported a 20% increase with multifocal IOLs; this study also pointed out more patient-reported discomfort in dim light conditions which potentially would affect night driving. Although this measure of straylight was statistically insignificant it was concluded that the straylight produced with multifocals adds to visual discomfort more rather than visual disability as shown by the significantly higher complaint scores from patients implanted with the AcrySOF ReSTOR IOL. Vries *et al* (2008) also investigated retinal straylight measurements in an apodized diffractive IOL and reported slightly higher levels with the multifocal lens group than monofocal group. Higher levels of intraocular straylight lead to higher sensitivity to glare (Van Den Berg, 1995).

There is controversy over patient satisfaction with multifocal IOLs as for example; a questionnaire completed one year following implantation of the Array multifocal highlighted three particular symptoms of glare, halos and blurry distance vision which were reported as significantly worse than with monofocal lenses (Steinert, 2000). These symptoms were described as 'severe' in 15% of cases for halos, 11% for glare and 4% for blurred distance vision. However, studies have shown such occurrence of photic phenomena does reduce with increasing time post-operatively (Vaquero-Ruano *et al.,* 1998) in a process of neuroadaptation (Voskresenskaya *et al*., 2010; Souza *et al.,* 2006).

Jacobi *et al* (1999) suggested asymmetric bilateral implantation of multifocal IOLs in order to enhance contrast sensitivity (mix and match technique) and intermediate vision where one diffractive IOL is implanted in one eye and a refractive IOL in the other. However compromises in distance and near vision result with loss of stereopsis (Voskresenskaya *et al.,* 2010). Other suggestions include aspheric designs with a lower additional power for near vision (Hayashi *et al*., 2009) however this may not provide sufficient near vision.

A clear requirement thus exists for improved intermediate vision with multifocal technology. Swanson (1994) developed a theoretical calculation for a diffractive lens to form three foci, where each focal point receives 28.8% of the incident light, and a residual 14% of light distributed to the other foci. Such a design, known as a trifocal lens, allows vision at intermediate distances without degrading vision in the distance or at near (Gatinel *et al.,* 2011). There are very few studies investigating this new concept of trifocal lenses. The first published findings were by Voskresenkaya *et al* (2010) where the visual outcomes of the MIOL-Record 3 (Reper-NN, Nizhegorodskaja Provinces, Russia) trifocal lens were investigated. The MIOL-Record consists of a stepped design diffractive optic, this lens significantly improved distance and near vision comparable to diffractive multifocal

IOLs (AcrySof ReSTOR, AcrySof Natural ReSTOR, Acri.Lisa 366D, ReZoom, Tecnis MF), as well as providing adequate intermediate vision of 0.66 ±0.22 at 50cm.

As there are three simultaneous foci with a trifocal lens, it may be argued that contrast sensitivity could be compromised further however Voskresenkaya *et al* (2010) found photopic contrast sensitivity to be comparable with that of monofocal IOLs. Mesopic contrast sensitivity however was indeed reduced in comparison to monofocal IOLs although this did not seem to affect patient satisfaction as 94% reported no or mild difficulty with vision at night. Glare and halos were also of acceptable levels as 75-94.5% of subjects did not find significant problems with such photic phenomena and also noticed a decrease with time following implantation leading to a significant decrease in complaints 3-6months post-operatively.

Gatinel *et al* (2011) described an aspheric fully diffractive IOL aiming to provide better intermediate vision and less photic phenomena which has been implemented into the Physiol FineVision IOL; optical bench testing has shown it to successfully provide these aims, but further clinical studies are required to validate its performance. The purpose of the present study was therefore to investigate the visual outcomes, measurement of glare, photopic and mesopic contrast sensitivity and the patient satisfaction with the Physiol FineVision trifocal diffractive intraocular lens.

7.2. Methods

7.2.1. Intraocular Lens Characteristics

Physiol FineVision is a four point haptic aspheric diffractive lens, made of hydrophilic acrylic with 25% water content, of bi-convex design (*Figure 7.1*). Three foci are achieved by a combination of two bifocal diffraction patterns of +1.75 dioptre addition for intermediate vision and +3.50 dioptre addition for near vision (*Figure 7.2*). The first diffraction pattern with the addition of +3.50 dioptres is the first diffraction order with a second diffraction order occurring at a vergence of 7 dioptres. The second pattern, with an addition of +1.75 dioptres as the first order has a second order which is twice the first diffractive order, resulting in +3.50 dioptres. Since the first and second orders of this second pattern equate to the intermediate and near powers of the IOL they contribute and enhance intermediate and near vision. Resulting light loss from this design is reduced to approximately 14% from a typical 18% with bifocal multifocal designs (Gatinel *et al.,* 2011). In photopic conditions 42% of incident light is used for distance foci, 29% for near and 15% for intermediate, with mesopic conditions 58% is distributed to distance, 20% for near and 8% for intermediate vision.

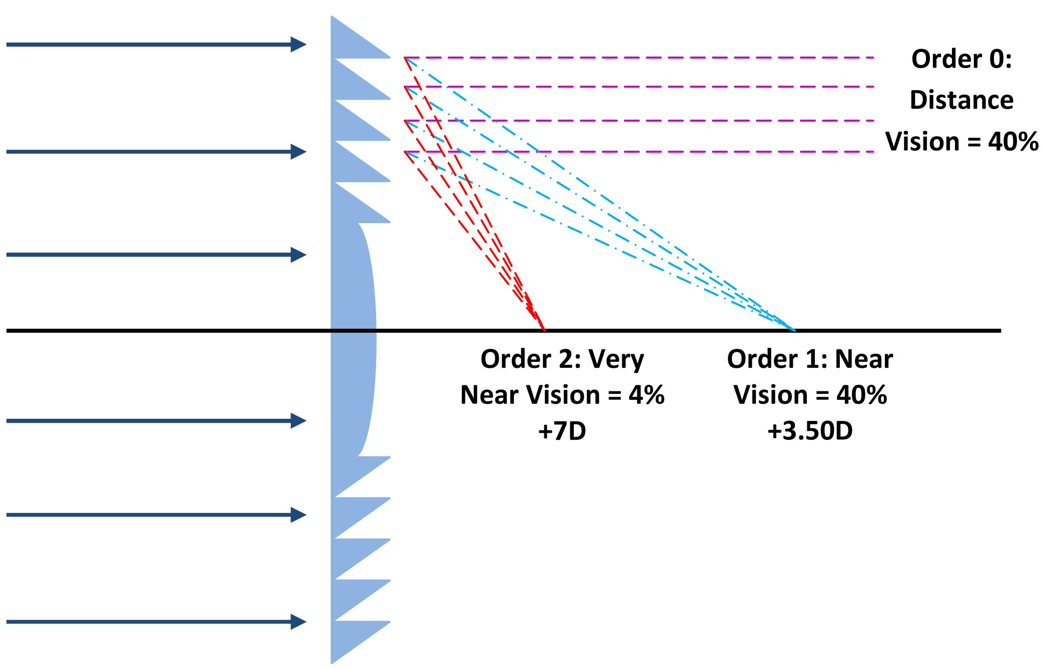
The IOL is apodized, where the step height reduces from the centre to the periphery of the lens optic. The design is pupil dependent; with pupil enlargement light enters through the peripheral areas of the IOL which is assigned to distance vision, reducing the amount of light reaching near and intermediate foci. The optic is entirely convoluted where a smoothing function has been implemented into the design to reduce the perception of haloes. The optic diameter is of 6.15mm with an overall diameter of 10.75mm. The IOL filters ultraviolet and blue light. There is also a four-point loop haptic design for increased stability. The powers available in this particular design range from +10 dioptres to +30 dioptres in 0.50 dioptre steps.

Figure 7.1: *FineVision trifocal diffractive IOL*

Aston University

Illustration removed for copyright restrictions

Figure 7.2: *Multiple foci of trifocal IOL*



7.2.2. Experimental Design

Thirty eyes of fifteen patients undergoing routine bilateral cataract extraction at the Midland Eye Institute, UK were implanted with the PhysIOL FINe Vision intraocular lens following informed consent. The study was approved by the Institutional Review Board and conformed to the tenets of the declaration of Helsinki. Participants were aged between 52-86 years, with a mean age of 69.8 ± 10.0 years, with bilateral senile cataracts. Exclusion criteria consisted of no retinal pathology or history of ocular infections, clear intraocular media, no previous ocular surgery or trauma, potential for BCVA of only 6/12 or worse. Good general physical and mental health was also required for participation in the study. The study consisted of an initial pre-operative visit of biometry measurements using the Zeiss IOLMaster and explanations regarding surgery and the proposed IOL implantation. Routine phacoemulsification surgical technique and IOL implantation was completed at the Midland Eye Institute, UK. Following surgery ocular health was again assessed to ensure no post-surgical complications had arisen. Second eye surgery took place 6 weeks following the initial operation.

Visual performance was assessed at a three months post-operative visit to assess the visual. Tests included;

- Monocular and Binocular UCDVA (logMAR)
- Subjective Refraction (maximum plus for best distance VA)
- Monocular and Binocular BCDVA
- Monocular defocus curves from +1.50D to -4.00D in 0.50D steps in photopic (85cd/m^2) conditions
- Binocular defocus curves from +1.50D to -4.00D in 0.50D steps, in photopic and mesopic (5 cd/m^2) conditions
- Contrast sensitivity measurement using the CSV-1000 test (VectorVision, Ohio, USA)
- Halometry glare test
- Completion of the NAVQ questionnaire

Defocus curve measurements consisted of recording visual acuity, using computerised logMAR progression Test Chart (Thomson Test Chart XPert, Thomson Software Solutions, Hertfordshire, UK), through random presentations of trial lenses from +1.50 dioptres to -4.00 dioptres over the refractive correction; this was repeated moncularly in photopic conditions and binocularly in both photopic and mesopic conditions. Pupil diameters were also measured in photopic and mesopic conditions. Letters were randomized as each trial lens was presented to avoid subjects memorizing the chart (Gupta *et al.,* 2007).

Photopic contrast sensitivity was recorded using the CSV-1000 contrast sensitivity chart at a distance of 2.5 meters. The chart comprises of 4 rows of 8 sine-wave gratings consisting of spatial frequencies 3, 6, 12 and 18 cycles/degree. The subject was instructed to indicate the direction of each sine gratings in each of the five rows until no longer resolved. The last correctly indentified grating in each row was recorded.

The Halometry glare test (Buckhurst *et al,.* 2011) used to measure the glare area for each patient, involved a central LED light source (colour temperature 3200K) placed centrally on a flat LCD screen on which letters were presented around the light source at eccentricity of 0, 45, 90, 135, 180, 225, 270, 315 degrees. Letters were presented at a height that subtended 0.21° at a working distance of 3 meters, equivalent to the minimum vision requirements for driving standards in Europe. The letters were presented on a black background at a contrast of 500 Weber contrast units (C_w) and presented along each of the eight meridians in 0.05° steps. Testing was conducted in a dark room monocularly and binocularly, letters were presented in a random order and randomized between presentations along each meridian from the centre. The closest point to the glare source, at which the patient correctly identified a letter, was recorded.

To assess subjective satisfaction with near vision function, patients completed a validated 10-item questionnaire; the Near Activity Visual Questionnaire (NAVQ), (Buckhurst *et al.,* 2012). The NAVQ is designed for the evaluation of presbyopic corrections, and requires patients to indicate their level of difficulty performing common near and intermediate vision tasks without the use of reading spectacles (where 0 = no difficulty, and 3 = extreme difficulty), and to rate overall satisfaction with their near vision (where 0 = completely satisfied, and 4 = completely unsatisfied). The summated score from the main body of 10 questions is adjusted to a Rasch score (from 0 to 100 Logits) using a conversion table, such that 0 indicates no difficulty at all with any near tasks, and 100 indicates extreme difficulty with all near activities.

7.3. Statistical Analysis

Monocular and binocular visual acuity measures were totalled and averaged for comparisons and defocus curve plots. Contrast sensitivity scores were also averaged with comparisons made between photopic and mesopic contrast sensitivity. All answers from the questionnaire were totalled and converted to a Rasch score to give the final questionnaire result. T-tests for measures of statistical significance were also performed.

7.4. Results

All patients underwent uneventful cataract surgery on both eyes, IOLs were well centred in all eyes, with no occurrence of pupil distortion or iris trauma. Details of the means and standard deviations of monocular and binocular distance visual acuities and distance vision efficacy are shown in *Table 7.1*. The mean monocular refractive correction was 0.27 ± 0.36 D sphere (range -0.25 to +1.00 D) and -0.48 ± 0.45 D cylinder (range 0 to -1.50 D). *Figure 7.3* shows the binocular mean defocus curves under photopic and mesopic conditions. In both lighting conditions, optimum visual acuity results were obtained at 0.00 D defocus which is equivalent to distance vision viewing, with a second "peak" at -2.50 D equivalent to near viewing at 40 cm. No distinct peak in the intermediate zone was present for either of the lighting levels, with no sharp drop in acuity in the intermediate zone for the photopic condition, although the range of clear vision (0.3 logMAR or better) extended from +1.00 to -2.50 D of defocus. The mean visual acuities were generally better in the photopic conditions, however the differences between lighting conditions were not significant, except at -1.50 D defocus ($p=0.008$), corresponding to an intermediate viewing distance.

Acuity		Number of eyes/ patients (%)	
	Mean ± SD	**0.3 logMAR or better**	**0.1 logMAR or better**
Monocular:			
UDVA	0.19 ± 0.09	24 eyes (80)	6 eyes (20)
CDVA	0.08 ± 0.08	30 eyes (100)	21 eyes (70)
Binocular:			
CDVA	0.06 ± 0.08	15 patients (100)	13 patients (87)

Table 7.1: *Monocular and binocular logMAR distance visual acuities 3 months following FineVision IOL implantation. UDVA = uncorrected distance visual acuity; CDVA = best-corrected distance visual acuity.*

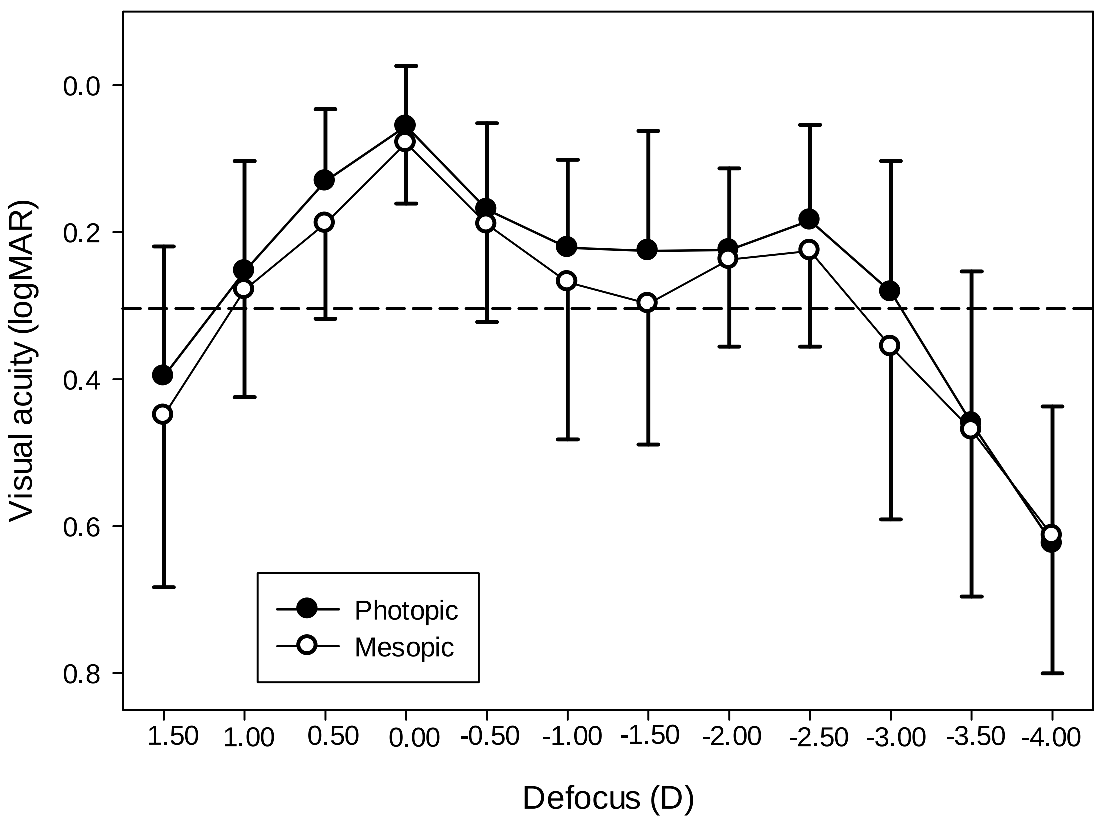


Figure 7.3. *Binocular mean defocus curves for the FineVision trifocal IOL in photopic and mesopic conditions. Error bars = ± 1 SD. The dotted reference line at 0.3 logMAR equates to the European driving standard.*

Figure 7.4 shows the monocular and binocular distance contrast sensitivity ($log_{10}CS$) under photopic conditions. Binocular contrast sensitivity values were significantly better than monocular values at all spatial frequencies tested ($p<0.05$). No significant differences in contrast sensitivity values between right and left eyes were found at any spatial frequency ($p> 0.05$).

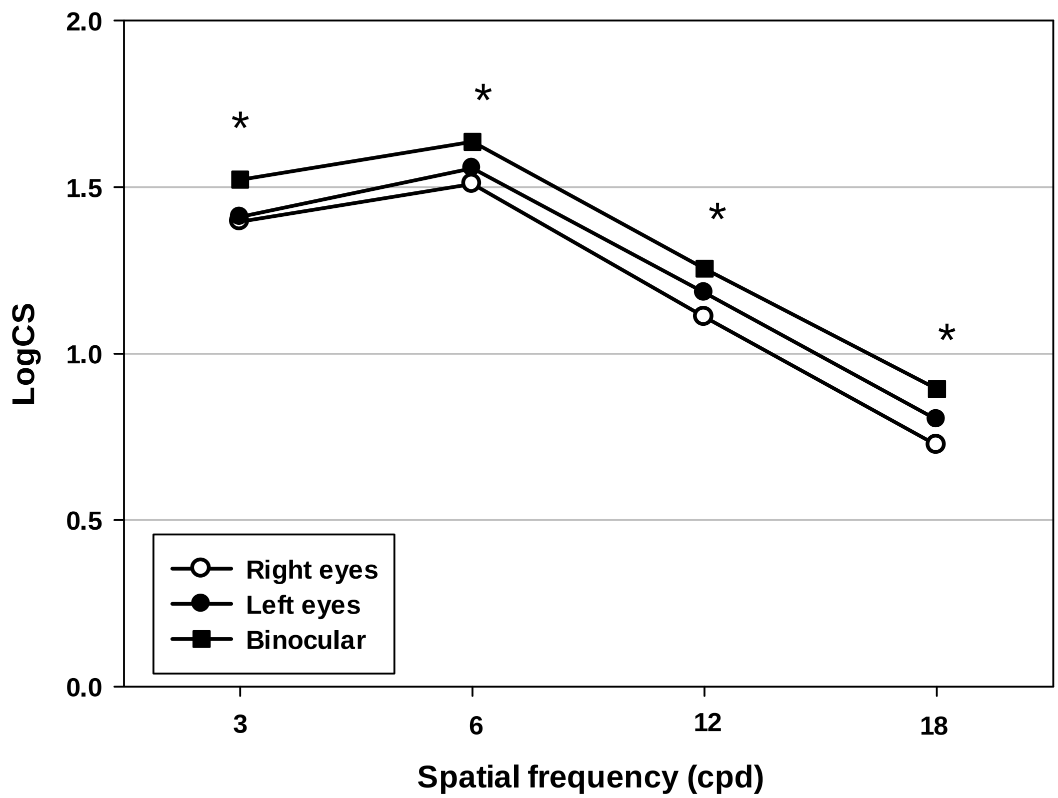


Figure 7.4. *Monocular and binocular contrast sensitivity functions with the FineVision trifocal IOL, under photopic conditions. * = statistically significant difference between monocular and binocular values.*

Figure 7.5 illustrates the halometry results, with the magnitude of the mean monocular and binocular photopic scotomas, measured under mesopic conditions shown. The mean photopic scotomas are generally uniform in shape, extended binocularly between 0.69 ± 0.24 degrees and 1.03 ± 0.20 degrees for all 8 meridians.

NAVQ scores for subjective satisfaction with near vision were high, with a mean Rasch score of 15.9 ± 10.7 Logits (0 = completely satisfied, 100 = completely unsatisfied; range 0 to 33.3). The final NAVQ item, rating overall satisfaction with near vision (0= completely satisfied, 4= completely unsatisfied) resulted in a mean score of 0.7 (range 0 to 2).

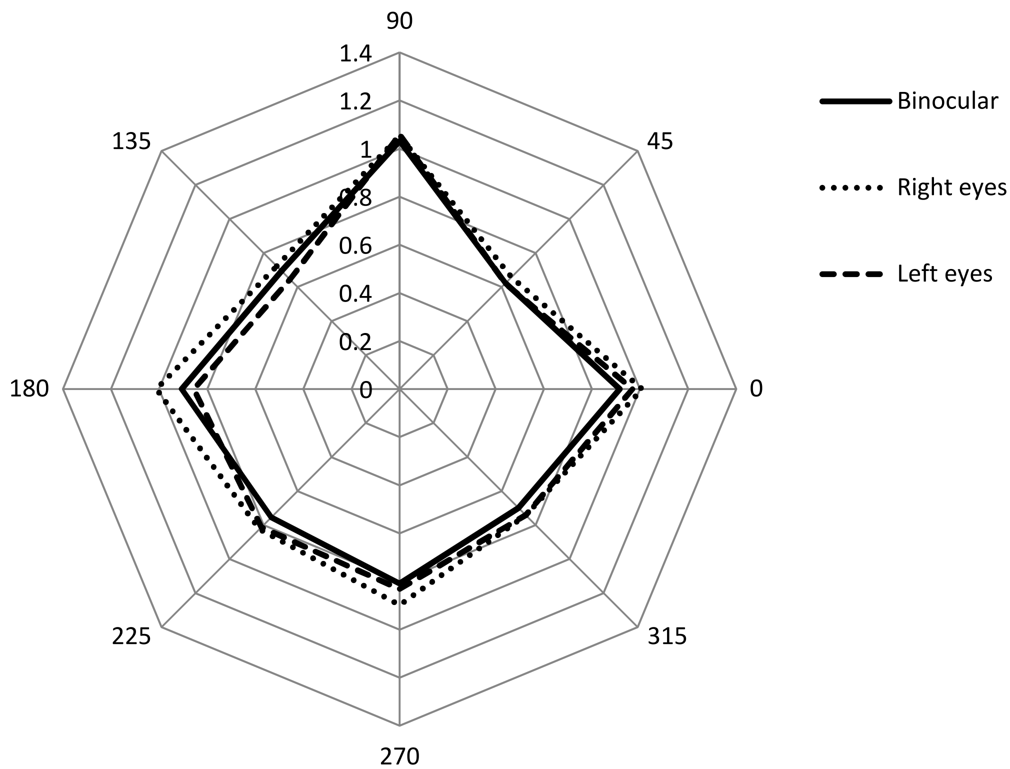


Figure 7.5: *Size of monocular and binocular photopic scotomas, measured using halometry under mesopic conditions. Y axis = extent of scotoma from glare source (degrees), radial axis = visual field meridian (degrees).*

7.5. Discussion

Multifocal IOLs are becoming more widely used as patients undergoing cataract surgery have increasing functional expectations and a desire for post-operative spectacle independence (Hawker *et al.,* 2005; Pager, 2004; Mũnoz *et al.,* 2011). Current diffractive multifocal IOLs typically provide good vision at distance and near (Zhang *et al.,* 2011; Munoz *et al.,* 2011; Alió *et al.,* 2008) but have the disadvantages of bifocal design, potentially leading to intermediate vision difficulties (Gatinal *et al.,* 2011; Voskresenskaya *et al.,* 2010). To the best of our knowledge, this is the first study to report clinical outcomes of a cohort implanted binocularly with a diffractive trifocal IOL design. The mean monocular UDVA (0.19 ± 0.09) and CDVA (0.08 ± 0.08) results are similar to the values reported by Voskresenskaya *et al* (2010) with predominantly monocular implantation of the MIOL-Record. Furthermore, the visual acuity outcomes were comparable to those achieved with several bifocal-design diffractive IOLs (Zhang *et al.,* 2011; Alió *et al.,* 2011, Alió *et al.,* 2008).

Binocular defocus curve testing indicated an extended range of clear vision. Although mean VA was 0.3 logMAR or better from +1.00 to -2.50 D defocus in both photopic and mesopic conditions, no obvious peak in VA was apparent in the intermediate zone. Such a finding may be expected, as a relatively small proportion of light is available for intermediate vision compared to distance and near. As pupil size increases, a greater proportion of light is directed to the distance focus due to the apodized optic, such that for a 5mm pupil, only approximately 5% of light is available for intermediate vision. The reduced light available for intermediate vision with larger pupil sizes is likely to be the cause of the significantly poorer visual acuity in mesopic compared to photopic conditions at -1.50 D defocus. No significant differences in VA between mesopic and photopic conditions were found at any of the other defocus levels tested.

With the FineVision IOL binocular contrast sensitivity values were significantly higher than monocular values at all spatial frequencies. The well-known effect of binocular summation explains the difference between monocular and binocular results, and is in agreement with previous reports of diffractive IOL outcomes, where several authors have advised binocular implantation to optimise contrast sensitivity (Jacobi *et al.,* 1999; Fernández-Vega *et al.,* 2007; Schmidinger *et al.,* 2005). Multifocal IOLs have previously been reported to cause up to a 50% reduction in contrast sensitivity (Pieh *et al.,* 1998), however, in this study monocular contrast sensitivity values were within the normal range for older adults as described by Pomerance and Evans (1994), although slightly below their mean values. Reasons for this may include the older cohort used in the present study (mean age 69.8± 10.0 years in the present study, compared to 63.9 ± 12.2 years for Pomerance and Evans) and normal age-related retinal and neural changes (Elliot 1987, Spear 1993).

Photic phenomena frequently associated with multifocal IOLs are approximately 3.5 times more common with multifocal compared to monofocal IOLs (Leyland and Zinicola, 2003) and may impact on quality of life (Javitt and Steinert, 2000). In the present study, no patients reported photic phenomena, suggesting that the design of the FineVision IOL, with increasing far vision dominance as pupil size increases, may be effective in minimizing halos and glare perception. However, a larger scale study would be required to gain a full insight into the frequency of adverse photic phenomena with the FineVision IOL. The mean size of the photopic scotomas (monocular extent from glare source ranged from 0.6 ± 0.3 to 1.1 ± 0.2 degrees) measured in the present study compares favourably with previous measures using the same technique and with another study investigating glare, on patients implanted with a multifocal and an accommodating IOL design (Berrow, *et al,.* 2012). The novel halometry technique used within the current study has not been used widely therefore comparisons with multifocal IOLs are limited. However previous straylight measurements using the CQuant straylight meter show straylight levels of 1.2 log units within a diffractive multifocal group (de Vries *et al.,* 2008) therefore showing much higher levels of halos and glare compared to the FineVision trifocal lens.

Subjective satisfaction with unaided near vision, as measured with the NAVQ questionnaire, was high in the present study (mean 15.9 ± 10.7 Logits). The NAVQ test (Buckhurst *et al.,* 2012) is designed to allow a more standardized comparison of presbyopia correction strategies, by questioning patients on their ability to perform common near tasks such as; reading post and seeing the display on a computer without an additional near vision correction. The mean value obtained with the FineVision trifocal IOL shows a higher level of patient satisfaction with near vision than reported by Buckhurst *et al*. (2012) for other multifocal and accommodating IOLs. The improved score with the FineVision compared to other presbyopia-correcting IOLs may be due in part to improved intermediate vision provided by the 1.75 D intermediate add as the NAVQ includes questions relating to intermediate-distance visual function, such as using a computer and performing hobbies such as gardening or playing cards.

A particular limitation in this investigation was the small sample size. Although the sample size efficiently demonstrated the advantages of trifocal design, a larger cohort would be required in order to validate these findings in a wider range of patients. Patients are usually happy following cataract surgery as limitations of the IOL optics are of less concern than the reduction in vision and light scatter caused by the cataract. However, the use of a validated near vision questionnaire at least allows comparison with other forms of presbyopic correction already evaluated.

7.6. Conclusion

In conclusion, the FineVision trifocal IOL provides a good standard of distance, intermediate and near visual function, as demonstrated by defocus curve testing. The increasing far vision dominance of the IOL as pupil size increases may be effective at reducing photic phenomena frequently associated with multifocal IOLs. Near vision satisfaction amongst this cohort of bilaterally-implanted patients was high, which along with the clinical measures, suggests that the FineVision IOL is an effective method of providing good distance, near and intermediate visual ability. However a greater cohort is required to appreciate the benefits of this new IOL design.

CHAPTER 8

Summary & Conclusions

8.1. Introduction

Since the introduction of intraocular lenses in the 1950s there have been vast developments in their design. Research initially concentrated on improving IOL materials to allow long-term stability within the eye and to remain transparent once implanted. In more recent years, focus has now changed to enhancing the optics of intraocular lenses to provide optimum vision following surgery. Such lenses, termed premium IOLs, aim to reduce astigmatism and provide correction for presbyopia. The health system of the U.K. currently implant basic spherical IOLs as the standard of care following cataract extraction as the cost of implantation of premium IOLs exceed that of what is currently available. Individuals seeking spectacle independence following cataract surgery or refractive lens exchange are often unaware of the options that premium lenses are able to offer. For patients that desire such lenses, payment of both the actual lens and private surgery fees would be required as no ‘top-up’ option is available through the National Health Service in the U.K.

As outlined in the introduction, although many advances have been made in IOL designs, the benefits of premium IOLs have not been well established, nor when they should be considered as an optical correction. Implanting advanced optical designs also raises more complex surgical issues relating to IOL rotation and centration which deserve attention to optimise the visual results. The present thesis therefore examined the benefits of astigmatic correction with a toric lens over the mean spherical equivalent and how pupil dilation influences the alignment of these lenses. Centration of IOLs during surgery and over the following 6 months was also examined. Better methods to measure residual accommodation were explored along with what factors, other than age, affect when an individual becomes presbyopic and therefore should consider elective IOL surgery with implantation of a premium IOL. Finally, the benefits of a new type of IOL, a trifocal diffractive design, was evaluated to determine the range of clear vision offered as well as the visual compromises experienced.

8.2. Summary

Chapter 2 indicated the negative effect of uncorrected astigmatism on a selection of daily activities in the elderly population. Performance of tasks reduced as simulated astigmatism increased in power from as low as 1 dioptre with deviation of the axis from the vertical further affecting visual ability. Contrast sensitivity was highly compromised by increasing levels of astigmatism which may present as difficulty in night driving and navigation. As a large proportion of patients already restrict their journeys in dark conditions post-cataract surgery, residual astigmatism will simply add to this effect. Individuals with spherical errors alone usually conform to driving standards following cataract surgery but uncorrected astigmats often do not without additional refractive correction which may restrict driving further due to lack of confidence through reduced vision.

In addition, the study showed significantly reduced reading acuity and reading speed with increases in astigmatic power. Reading is of paramount importance in the elderly population often due to restrictions in mobility. Furthermore, it has been iterated that visual demands particularly for near work are continuously rising with developments in technology and communication, the use of which is increasing within elderly populations. Despite the lack of a mobile lens in presbyopia already impacting on near vision, this will be exacerbated by effects of astigmatism. The subjective ratings of clarity within the study highlighted the awareness of individuals of that poor vision.

Collectively, such restrictions in the ability to perform the daily tasks described will lead to a significant reduction in quality of life as well as increased risk of falls and possible risks to driving safety. Chapter 2 therefore outlined the potential benefits that premium lenses such as toric IOLs may provide to patients through improvements in quality of life. The study also supports toric implantation as standard care for cataracts by public health services as it is suggested that the cost of implantation would outweigh the consequences of residual uncorrected astigmatism.

Implanting toric IOLs, however, raises speculation of rotational stability. For a successful visual outcome, toric IOLs require high precision on alignment from surgeons. As there is currently no standardised procedure for alignment of such premium intraocular lenses, Chapter 3 therefore examined the effect of dilation on newer, more robust imaging techniques for toric IOL alignment which rely on either iris features of conjunctival blood vessels on either side of the iris to compensate for head rotation when examining IOL orientation. The development of more complicated optics for correction of presbyopia following cataract surgery requires more precise and diligent techniques of implantation. Pupil dilation is imperative in cataract and refractive lens surgery although it has been associated with changes in pupil centration which could impact alignment. Current positioning techniques however are crude and may lead to misalignment along with central dislocation due to deviation in pupil centre on dilation.

Assessment of iris features and conjunctival vessels with various degrees of dilation showed the latter as a more stable landmark for use in IOL alignment. Head tilt has been considered as a possible source of error in pre-operative marking for toric implants, however, the current investigation showed little disturbance to measures by head movement suggesting that a slit lamp head rest provides sufficient stability. Pupil diameter increased in a sigmoidal pattern moving more inferiorly through dilation. On average the pupil, prior to dilation, is located slightly supero-nasal, the limbus measures showed negligible changes in its position on repeated measures suggesting the pupil to be an unreliable structure for alignment procedures. Surgeons may thus find use of the limbus as a reference structure in such proceedings more beneficial in addition to conjunctival vessels as markers for alignment. As previously discussed only young subjects were recruited for the study therefore repeating the investigation with an older cohort may provide further knowledge as to how dilation affects mature pupils. Such information may prove beneficial as premium IOLs are generally fitted in older age groups.

Future studies could expand this research by investigating the differences between pupil location in different coloured irides to establish if the effect of dilation in pupil decentration is more pronounced in dark or light irides. Such information may then be accounted by surgeons in order to achieve the best possible surgical outcome with premium IOLs. Scheimpflug imaging may be another way to determine movement changes in IOL centration with respect to the pupil along with additional information on IOL tilt, with time. Moreover, future research could explore if minor decentration contributes to visual phenomena with multifocal IOLs.

Chapter 3 therefore clearly established the significant changes of pupil centration and surface features during pre-operative dilation and how this may affect the implantation of premium IOLs. However, the possible effect on the pupil following cataract surgery has not been considered in the performance of premium IOLs, Chapter 4 thus extended this by examining the post-operative effect on pupils six months after cataract extraction and IOL implantation. Early investigations by Gibbens *et al* (1989) had reported on pupil changes following suggestions of reduced pupil diameter with ICCE and ECCE procedures. Since then cataract surgery has advanced considerably and no previous research has investigated such post-operative effects with newer phacoemulsification techniques. As post-operative complications have reduced in magnitude since the evolution of cataract extraction, it would be assumed that little impairment to pupil function would occur. On the contrary, chapter 4 describes post-operative inferior movement of the pupil centre but no horizontal displacement. Pupils became more oval with time and the maximum diameter following dilation showed significant reduction. These changes tended to become more apparent much later after surgery rather than immediately following surgery. Interestingly, IOL centration remained stable with respect to the limbus but showed vertical displacement when compared to the pupil. Such findings suggest that the pupil must alter its position whilst in fact the IOL remains stable. In relation to premium IOLs this information emphasizes the need for a more stable structure to assist surgeons with the centration of premium IOLs. Complexity in their optical designs may present considerable visual disturbances if inaccurately centred. It is therefore again confirmed that the limbus offers a more suitable guide for IOL alignment. The investigation further suggests post-operative changes in pupil structure may interfere with the performance of premium IOLs regardless of initial positioning, indicating the requirement for further research into post-operative alignment of premium IOLs.

Comparisons and measurements of diameters prior to surgery were not made, which may have provided some information to the variation found within chapter 4 and provides scope for further research. Permeability of the cornea could also be examined in order to investigate if this contributes to the differences in pupil diameter following surgery. In addition, advanced high resolution imaging of the iris may aid further research into where damage may occur to the iris structure to result in only vertical shifts of the pupil centre.

Spectacle independence and correction of presbyopia remain the penultimate aim of premium IOLs to which there is a rising interest for refractive lens exchange amongst patients approaching presbyopia. Age has already been deemed as the greatest factor contributing to presbyopia. However, earlier work from various researchers introduced the concept of environmental factors influencing amplitude of accommodation and hence the age of onset of presbyopia. Climate, increased sunlight and environmental temperature presented as common findings affecting accommodation and leading to early presbyopia, giving the general agreement that populations inhabiting near the equator exhibited lower amplitudes of accommodation and developed presbyopia much earlier than clinically expected.

Chapter 5 explored the amplitude of accommodation and onset of presbyopia in a population within the United Kingdom. Questioning on lifestyle and measurements of accommodation has shown many factors may contribute to the rate of progression of presbyopia in addition to age, in particular; alcohol consumption, smoking, UV exposure, weight and even use of VDUs and mobile communication. Knowledge of factors which may indicate the rate of progression to presbyopia allows estimates of an individual's age of presbyopia onset to be made. Such knowledge will aid better communication when discussing the changes that would occur with patients considering a premium IOL clear lens extraction.

Within this thesis, the average presbyopia onset was calculated as approximately 48 years. Cataracts typically form later than this, but patients should be provided with all the relevant information to them which should include advice on premium IOL implantation, removing the need for further cataract surgery in later years. Chapter 5 has thus shown despite improvements in health, diet and medicine, aspects of modern lifestyle may still increase the rate of presbyopia hence warranting the need of presbyopia correcting solutions which may be addressed by premium IOLs, as no significant factors have shown to reverse or reduce the effect of presbyopia.

Further assessment of lifestyle and environmental factors on a more global scale may be carried out as little information exists on this area of research. To avoid bias of information given by the patients to questionnaires, data for dietary information could be collected prospectively using food diaries and blood samples. Information gathered through such procedures would provide better determination of vitamin intake as the food and supplements consumed does not necessarily correlate to nutrition actually absorbed into the bloodstream. Further research proposes to revise the work of Donders (1864) and Duane (1909, 1912) using more objective measurements of accommodation rather than subjective. As previously highlighted the primary limitation of this chapter was the use of subjective measurement of amplitude of accommodation. Despite combining push-up and pull-down results, the values obtained may still present higher readings due to depth of focus. Chapter 6 outlined the inadequacies of the RAF rule in providing reliable measurements of accommodation and how new technology may be able to overcome the limitations of the standard push-up technique with the RAF rule.

It is important to investigate how much near vision range is gained through presbyopia correcting procedures, such as implantation of premium lenses, in order to assess their level of benefit. To accurately measure this, a better subjective technique is required than those that currently exist. The preference for subjective techniques, for the assessment of premium lenses, in combination with objective measures is attributed to their presentation of functional vision. Functional vision is in association with the patient's perceived vision, ultimately showing greater importance in addition to what is clinically gained. Evaluating and formulating a new method of assessing subjective amplitude of accommodation would allow better assessment of accommodation following various procedures aimed at restoration of accommodation. Improved assessment of visual symptoms on near task performance would also be accomplished by such technology. The development and validation of an electronic accommodometer aimed to fulfil these suggestions by introducing an automatically adjustable target, which subtended the same visual angle and illumination upon push-up and pull-down measurement. In comparison to measurements of the RAF rule the accommodometer demonstrated higher amplitudes of accommodation but these were found to be statistically insignificant. Repeatability of both instruments was acceptable and similar. The RAF rule and accommodometer, however, showed differences in comparison to the minus lens technique which may be attributed to differences in target distance. With minus lenses minification of targets is induced and accommodative demand is increased, conversely, with push-up tests targets become larger and accommodative demand is decreased.

Further research in this field includes the development of a new modified accommodometer incorporated into a Smartphone; which would provide a more compact form of measuring accommodation and would reduce the time delay leading to erroneous detection and over-estimated output.

Premium IOLs may effectively improve functional vision at near with exceptional distance vision and thus fulfil the requirement of correcting refractive errors and presbyopia. Despite good levels of distance and near vision with multifocal IOLs, poorer intermediate visual acuity hinders aims of spectacle independence. In addition photic phenomena are of concern with these premium IOLs. In attempts to provide improved intermediate vision with diffractive multifocal designs an IOL producing three points of focus has been conceptualized, as conventional multifocal IOLs have been shown to have a significant drop in visual acuity for intermediate distance viewing. Restrictions of visual function at this distance not only limits work on VDUs but other tasks and hobbies such as reading music. To achieve multiple foci the trifocal design shares incident light amongst three foci with the aim of not compromising the distance and near images formed.

Assessment of the PhysIOL FineVision intraocular lens in Chapter 7, showed acceptable visual acuity which conformed to European driving standards. Visual acuity, as expected, was generally better in photopic conditions. Defocus testing gave a peak for distance vision and strong second peak depicting near vision at 40cm, however, no sharp peaks were attained for intermediate vision and performance at this distance was better than is generally seen with effectively bifocal IOL designs.

Being diffractive in nature the trifocal lens could be expected to display compromise in contrast sensitivity; binocular contrast sensitivity was significantly improved compared to monocular values and were within normal range. Halometry findings recognized the presence of photic phenomena within the trifocal design, however the finding were similar to other non-multifocal optical designs, no reports of glare or haloes were received from patients and levels of satisfaction were high. This suggests the combination of apodized design and distant dominance provides some reduction in glare and halo perception.

Proposals for expanding research would be direct comparisons of visual performance between groups implanted with a trifocal IOL and another with a conventional multifocal providing only two foci.

8.3. Conclusion

In conclusion this thesis has demonstrated the benefits of as well as the challenges of implanting premium IOLs which aim to correct astigmatism and presbyopia. The price of premium products reduces the more that are sold, as the research and development costs can be spread more widely. If they offer significant patient benefits, deals should be considered to make them the standard lens of choice. While correction of refractive errors can be worked, it is ideal and desirable to overcome uncorrected astigmatism or presbyopia, as this can impact on quality of life and is also linked to costly incidents such as changes in driving performance and falls. Patients are also currently poorly informed as to the options available to them and this needs to be communicated to them at the appropriate time so they can be directly involved in their health management. Industry is continuing to invest in new IOLs to provide a better quality of all round vision and this thesis contributes to the exciting future for optimizing vision in the elderly, a critical sense in maintaining our quality of life.

REFERENCES

Abbey A, Ide T, Kymionis G D, Yoo S H (2009) Femtosecond laser-assisted astigmatic keratotomy in naturally occurring high astigmatism. *British Journal of Ophthalmology*. 93:12, 1566-1569.

Abrahamson IA (1984) Eye changes after forty. *Am Fam Physician.* 29, 171-181.

Accommodating IOLs: What are They? Your-eye-sight.org (2009) [online image] Available at: http://www.your-eye-sight.org/accommodating-iols.html [Accessed: 20 Nov 2012].

Ahmed IIK, Rocha G, Slomovic AR, Climenhaga H, Gohill J, Grégoire A, Ma J (2010) Visual function and patient experience after bilateral implantation of toric intraocular lenses. *J Cataract Refract Surg.* 36, 609-616.

Ajayi OB, George OG (2007) Acute effect of caffeine on amplitude of accommodation and near point of convergence. *West J Pharmacol Drug Res.* 22/23, 27-30.

Akkin C, Ozler SA, Mentes J (1994) Tilt and decentration of bag-fixed intraocular lenses: A comparative study between capsulorhexis and envelope techniques. *Doc Ophthalmol.* 87, 199-209.

Alfonso JE, Fernandez-Vega L, Valcarcel B, Montes-Mico R (2008) Visual performance after AcrySof ReSTOR aspheric intraocular lens implantation. *J Optom.* 1:1, 30-35.

Alfonso JF, Fernandez-Vega L, Begoña Baamonde, Montés-Micó R (2007) Prospective visual evaluation of apodized diffractive intraocular lenses. *J Cataract Refract Surg.* 33, 1235-1243.

Alfonso JF, Fernandez-Vega L, Begoña Baamonde, Montés-Micó R (2007) Correlation of pupil size with visual acuity and contrast sensitivity after implantation of an apodized diffractive intraocular lens. *J Cataract Refract Surg.* 33, 430-438.

Alio JL, Ben-Nun J, Rodriguez-Prats JL, et al. (2009) Visual and accommodative outcomes 1 year after implantation of an accommodating intraocular lens based on a new concept. *J Cataract Refract Surg.* 35, 1671–1678.

Alió JL, Elkady B, Ortiz D, Bernabeu G (2008) Clinical outcomes and intraocular optical quality of a diffractive multifocal intraocular lens with asymmetrical light distribution*. J Cataract Refract Surg*. 34, 942-948.

Alió JL, Plaza-Puche AB, Piñero DP, Amparo F, Jiménez R, Rodríguez-Prats JL, Javaloy J, and Pongo V (2011) Optical analysis, reading performance, and quality-of-life evaluation after implantation of a diffractive multifocal intraocular lens*. J Cataract Refract Surg*. 37, 27-37.

Altman GE, Nichamin, LD, Lane SS, Pepose JS (2005) Optical performance of 3 intraocular lens designs in the presence of decentration. *J Cataract Refract Surg.* 31, 574-585.

Amesbury EC, Miller KM (2009) Correction of astigmatism at the time of cataract surgery. *Curr Opin Ophthalmol.* 20, 19–24.

Andley UP (2008) The Lens Epithelium: Focus on the expression and function of the α-crystalline chaperones. *Int J Biochem Cell Biol.* 40, 317-323.

Apple DJ, Sims J (1996) Harold Ridley and the invention of the intraocular lens. *Surv Ophthalmol.* 40, 279-292.

Arens B, Freudenthaler N, Quentin CD (1999) Binocular function after bilateral implantation of monofocal and refractive multifocal intraocular lenses. *J Cataract Refract Surg.* 25, 399-404.

Artal P (1990) Calculations of two-dimensional foveal retinal images in real eyes. *J Opt Soc Am (A).* 7, 1374-1381.

Atchison DA (1989) Optical design of intraocular lenses. III. On-axis performance in the presence of lens displacement. *Optom & Vis Sci.* 66:10, 671-681.

Atchison DA (1991) Design of aspheric intraocular lenses. *Ophthal Physiol Opt.* 11, 137–146.

Atchison DA (1995) Accommodation & Presbyopia. *Ophthal Physiol Opt.* 15:4, 255-272.

Atchison DA, Capper EJ, McCabe KL (1994) Critical subjective measurement of amplitude of accommodation. *Optom & Vis Sci.* 71:11, 699-706.

Atona B, Barra F, Barrio A, Gonzalez E, Sanchez I (2009) Repeatability Intraexaminer and Agreement in Amplitude of Accommodation Measurements. *Graefes Arch Clin Exp Ophthalmol.* 247, 121-127.

Awwad ST, Warmerdam D, Bowman W, et al. (2008) Contrast sensitivity and higher order aberrations in eyes implanted with AcrySof IQ SN60WF and AcrySof SN60AT intraocular lenses. *J Refract Surg.* 24, 619-625.

Bacskulin A, Gast R, Bergmann U, et al. (1996) Ultrasound biomicroscopy imaging of accommodative configuration changes in the presbyopic ciliary body. *Ophthalmologe.* 93, 199–203.

Balasubramanian D, Shalini VK, Luthra M, et al. (1993) Molecular epidemiology of the smoke cataract connection. Oxidant Stress Mechanism. *Invest Ophthalmol Vis Sci.* abstract 2925.

Bamashmus M (2010) Traditional Arabic Technique of Couching for Cataract Treatment in Yemen. *Eur J Ophthalmol*. 20:2, 340-4.

Barbero S, Marcos S, Jimenez-Alfaro I (2003) Optical aberrations of intraocular lenses measured in vivo and in vitro. *J Opt Soc Am A Opt Image Sci Vis.* 20, 1841-1851.

Barraquer RI, Michael R, Abreu R, et al. (2006) Human lens capsule thickness as a function of age and location along the saggital lens perimeter. *Invest Ophthalmol Vis Sci.* 47, 2053-2060.

Baumeister M, Buhren J, Kohnen (2009) Tilt and decentration of spherical and aspheric intraocular lenses: effect on higher-order aberrations. *J Cataract Refract Surg.* 35, 1006-1012.

Baumeister M, Neidhardt B, Strobel J, Kohnen T (2005) Tilt and decentration of three-piece foldable high-refractive silicone and hydrophobic acrylic intraocular lenses with 6mm optics in an intraindividual comparison. *Am J Ophthalmol.* 140, 1051-1058.

Bellucci R, Scialdone A, Buratto L et al. (2005) Visual acuity and contrast sensitivity comparison between Tecnis and AcrySof SA60AT intraocular lenses. *J Cataract Refract Surg.* 31, 712–17, errata 1857.

Benz PH, Ors JA (2007) A new approach to blue filtering intraocular lens materials. *Benz Res & Develop.* 46, 55-58.

Berdeaux G, Viala M, Roborel de Climens, et al. (2008) Patient-reported benefit of ReSTOR multi-focal intraocular lenses after cataract surgery: results of principal component analysis on clinical trial data. *Health and Quality of Life Outcomes.* 6:10, 1-9.

Berens C, Fonda GA (1950) A Spanish-English accommodation and near-test card using photoreduced type. *Am J Ophthalmol*. 33, 1788-1792.

Berens C, Stark EK (1932) Studies in ocular fatigue: IV. Fatigue of accommodation experimental and clinical observations. *Am J Ophthalmol.* 15, 527-542.

Bergmanson JPG, Söderberg PG (1995) The significance of ultraviolet radiation for eye diseases. *Ophthal Physiol Opt.* 15, 83-91.

Bergqvist U (1989) Possible health effects of working with VDUs. *Br J Ind Med.* 46, 217-221.

Berrow EJ, Shah S, Wolffsohn JS, Sheppard AL, Bhatt U, Bhogal G, Buckhurst P (2012) Binocular visual outcome of combining a segmented multifocal with an accommodating intraocular lens. *Presented at the Association for Research in Vision and Ophthalmology. 7th May 2012, Fort Lauderdale, FL*.

Black A, Wood J (2005) Vision and falls. *Clin Exp Optom*. 88, 212-222.

Bland J, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1-8476: 307-310.

Blaylock JF, Si Z, Vickers C (2006) Visual and Refractive status at different focal distances after implantation of the ReSTOR multifocal intraocular lens. *J Cataract Refract Surg.* 32, 1464-1473.

Bordonaba MC, Alvarez-Rementeria Fernandez L (2009) Marking the axis for toric IOL implantation. *Cataract & Refract Surg Today Eur*. 27-28.

Boulton M, Rozanowska M, Rozanowski B (2001) Retinal photodamage. *J Photochem Photobiol B.* 64, 144–61.

Brockmann C, Schulz M, Laube T (2008) Transmittance characteristics of ultraviolet and blue-light-filtering intraocular lenses. *J Cataract Refract Surg.* 34, 1161-1166.

Bron AJ, Sparrow J, Brown NAP, Harding JJ, Blakytny R (1993) The lens in diabetes. *Eye.* 7, 260-275.

Bron AJ, Tripathi R, Tripathi B (1997) Wolff's Anatomy of the Eye and Orbit. 8th ed. *Chapman & Hall Medical*. London. 414-415.

Brooks JO, Tyrrell RA, Frank TA (2005) The effects of severe visual challenges on steering performance in visually healthy young drivers. *Optom Vis Sci*. 82, 689-697.

Brown NAP, Hungerford J (1982) The influence of the size of the lens in ocular disease. *Trans Ophthalmol Soc UK.* 102, 359-363.

Brozek J, Simonson E, Bushard WJ, Peterson JH (1948) Effects of practice and the consistency of repeated measurements of accommodation and vergence. *Am J Ophthalmol.* 31, 191-198.

Bucci AF (2006) Asymmetric implantation of multifocal IOLs may improve visual comfort in patients with cataracts and presbyopia. *Eurotimes.* 11, 9-16.

Buckhurst PJ, Wolffsohn JS, Shah S, Naroo S, Davies LN (2011) Evaluation of Dysphotopsia with Multifocal Intraocular Lenses. *Presented at the Association for Research in Vision and Ophthalmology. May 2011*, *Fort Lauderdale, FL*.

Buckhurst PJ, Naroo SA, Shah S (2010a) Advanced intraocular lens design. *European Ophthalmic Review.* 4, 2-6

Buckhurst PJ, Wolffsohn JS, Davies LN, Naroo SA (2010b) Surgical correction of astigmatism during cataract surgery. *Clin Exp Optom.* 93:6, 409-418

Buckhurst PJ, Wolffsohn JS, Gupta N, Naroo SA, Davies LN, Shah S (2012) Development of a questionnaire to assess the relative subjective benefits of presbyopia correction*. J Cataract Refract Surg*. 38, 74-79.

Buckhurst PJ, Wolffsohn JS, Naroo SA (2010c) Rotational and centration stability of the aspheric Akreos AO intraocular lens. *J Cataract Refract Surg.* 36:9, 1523-1528.

Buckhurst PJ, Wolffsohn JS, Shah S, Naroo SA, Davies LN, Berrow EJ (2009) A new optical low coherence reflectometry device for ocular biometry in cataract patients. *Br J Ophthalmol.* 93, 949-53.

Buckhurst PJ, Wolffsohn JSW, Naroo SA, Davies LN (2010d) Rotational and centration stability of an aspheric intraocular lens with a simulated toric design. *J Cataract Surg.* 36, 1523-1528.

Budak K, Khater T, Friedman N, Holladay JT, Koch DD (1999) Evaluation of relationships among refractive and topographic parameters. *J Cataract Refract Surg.* 25, 814-819.

Burd HJ, Judge SJ, Cross JA (2002) Numerical modeling of the accommodating lens. *Vis Res.* 42, 2235-2251.

Burke AG, Patel I, Munoz B, Kayongoya A, Mchiwa W, Schwarzwalder AW, West SK (2006) Population-based study of presbyopia in rural Tanzania. *Ophthalmology.* 113, 723-727.

Caballero A, Losada M, Lopez JM, Gallego L, Sulla O, Lopez C (1991) Decentration of intraocular lenses implanted after intercapsular cataract extraction (envelope technique). *J Cataract Refract Surg.* 17, 330-334.

Cahill GF Jr (1979) Current concepts of diabetic complications with emphasis on hereditary factors: A brief review. *Prog Clin Biol Res*. 32, 113-125.

Calhounvision.com (n.d.) [online image] Available at: http://www.calhounvision.com/userfiles/images/CV_MECHANISM-OF-POWER_REVb_R4_Final.jpg [Accessed: 19 Nov 2012].

Campbell FW, Gubisch RW (1966) Optical quality of the human eye. *J Physiol (Lond).* 186, 558-578.

Campbell H, Doughty MJ, Heron G, Ackerley RG (2001) Influence of chronic alcohol abuse and ensuing forced abstinence on static subjective accommodation function in humans. *Ophthal Pysiol Opt.* 21:3, 197-205.

Carlson NB, Kurtz D, Heath DA and Hines C (1990) Clinical Procedures for Ocular Examination, Appleton & Lange, Norwalk CT, USA, pp11-12Strenk SA, Semmlow JL, Strenk LM, *et al* (1999) Age-related changes in human ciliary muscleand lens: a magnetic resonance imaging study. *Invest Ophthalmol Vis Sci.* 40, 1162–1169.

Carnevali T, Southnphanh (2005) A retrospective study on presbyopia onset and progression in a Hispanic population. *Optometry.* 76:1, 37-46.

Castejon-Mochon JF, Lopez-Gil N, Benito A, Artal P (2002) Ocular wave-front aberration statistics in a normal young population. *Vision Res.* 42, 1611-1617

Cataract Causes and Types Reclaimyourvision.com (1936) [online image] Available at: http://www.reclaimyourvision.com/what-causes-cataracts.aspx [Accessed: 11 Nov 2012].

Cekic O (1998) Effect of cigarette smoking on copper, lead and cadium accumulation in human lens. *Br J Ophthalmol.* 82, 186-188.

Chalita MR, Chavala S, Xu M, Krueger RR (2004) Wavefront analysis in post-LASIK eyes and its correlation with visual symptoms, refraction, and topography. *Ophthalmology.* 111, 447-453.

Chalita MR, Xu M, Krueger RR (2003) Correlation of aberrations with visual symptoms using wavefront analysis in eyes after laser in situ keratomileusis. *J Refract Surg.* 19, S682-686.

Charman WN, Walsh G (1989) Variations in the local refractive correction of the eye across its entrance pupil. Optom & Vis Sci. 66, 34-40.

Chiam PJT, Chan JH, Aggarwal RK, Kasaby S (2006) ReSTOR intraocular lens implantation in cataract surgery: quality of vision. *J Cataract Refract Surg*. 32, 1459-1463.

Chicago LASIK, Downtown Chicago Vision Correction, The Synchrony Lens Doctorsforvisualfreedom.com (2010) [online image] Available at: http://www.doctorsforvisualfreedom.com/synchrony-lens.html [Accessed: 20 Nov 2012].

Choi J, Schwiegerling J (2008) Optical performance measurement and night driving simulation of ReSTOR, ReZoom, and Tecnis multifocal intraocular lenses in a model eye. *J Refract Surg.* 24, 218-222.

Choi SK, Kim JH, Lee D, Park SH, Maeda N, Jung K (2010) IOL Tilt and Decentration (letter to editor). *Ophthalmology.* 117:9, 1862-1862.e4.

Christen WG, Manson JE, Seddon JM, Glynn RJ, Buring JE, Rosner B, Hennekens CH (1992) A Prospective Study of Cigarette smoking and Risk of Cataract in Men. *JAMA*. 268:8, 989-993.

Cook CA, Koretz JF, Pfahnl A, Hyun J, Kaufman PL (1994) Aging of the human crystalline lens and anterior segment. *Vision Res.* 34:22, 2945-2954.

Cook CS, McGahan, MC (1986) Copper Concentration in Cornea, Iris, Normal and Cataractous Lenses and Intraocular fluids of Vertebrates. *Curr Eye Res.* 5, 69-77.

Covell LL (1950) Presbyopia. Comparative observations of white and negro populations. *Am J Ophthalmol.* 33:8, 1275-1276.

Cronje S, Harris WF (1999) A comparison of keratometric variation in manual and automated keratometry. *South African Optometrist.* 58, 31-38.

Cumming RG, Mitchell P, Lim R (2000) Iris color and cataract: the blue mountains eye study. *Am J Ophthalmol.* 130, 237-238.

Dardzhikova A, Shah CR, Gimbel HV (2009) Early experience with the Acrysof toric IOL for the correction of astigmatism in cataract surgery. *Can J Ophthalmol.* 44:3, 269-273.

David G, Humphrey JD (2007) Finite element model of stresses in the anterior lens capsule of the eye. *Computer Methods in Biomechanics and Biomedical Engineering.* 10:3, 237-243.

Davson H (1990) Davson’s physiology of the eye. *Pregamon Press,* New York.

De Castro A, Rosales P, Marcos S (2007) Tilt and decentration of intraocular lenses in vivo from Purkinje and Scheimpflug imaging: Validation Study. *J Cataract Refract Surg.* 33, 418-429.

Dcareaeyecare.com (n.d.) [online image] Available at: http://www.dcareaeyecare.com/articles/5w_astigmatism_modelx300.jpg [Accessed: 2 Dec 2012].

Deaver DM, Davis J, Sliney DH (1996) Vertical visual fields-of-view in outdoor daylight. *Lasers Light Ophthalmol.* 7, 121-125.

Delcourt C, Carrière I, Ponton-Sanchez A, Lacroux A, Covacho MJ, Papoz L, POLA study group (2000) Light exposure and the risk of cortical, nuclear and posterior subcapsular cataracts. *Arch Ophthalmol.* 118, 385-392.

De Vries NE, Franssen L, Wbers CAB, Tahzib NG, Cheng YYY, Hendrikse F, Tjia KF, Van Den Berg T, Nuijts R (2008) Intraocular straylight after implantation of the multifocal AcrySof ReSTOR SA60D3 diffractive intraocular lens. *J Cataract Refract Surg.* 34, 957-962.

Doane JF (2004) Accommodating intraocular lenses. *Curr Opin Ophthalmol.* 15:1, 16-21.

Donders FC (1864) On the anomalies of accommodation and refraction of the eye: with a preliminary essay on physiological dioptrics, translated by William Daniel Moore*. The New Sydenham society*, London.

Duane A (1925) Subnormal Accommodation. *Arch Ophthalmol.* 54, 566-587.

Duane A (1909) The accommodation and Donders' Curve and the need to revising our ideas regarding them. *J Am Med Assoc.* 52, 1992-1996.

Duane A (1912) Normal values of the amplitude of accommodation at all ages. *J Am Med Assoc. 59,* 1010-1013.

Duane A (1922) Studies in monocular and binocular accommodation with their clinical applications. *Am J Ophthalmol.* 5, 865-877.

Duane A (1925) Are current theories of accommodation correct? *Am J Ophthalmol.* 8, 196-202.

Dubbelman M, van der Heijde GL, Weeber HA (2001) The thickness of the aging human lens obtained from corrected Scheimpflug images. *Optom Vis Sci.* 78:6, 411-416

Dubbelman M, van der Heijde GL, Weeber HA (2005) Change in shape of the ageing human crystalline lens with accommodation. *Vision Res.* 45, 117-132

Duke-Elder WS (1926) The Pathological Action of Light Upon the Eye. Action on the Outer Eye: *photophthalmia.* Lancet. 210 (5363), 1137-1141.

Duke-Elder WS (1954) Radiational Injuries, in *Textbook of Ophthalmology,* vol 6. St. Louis. The CV Mosby Company, 6443-6579.

Duncan G, Marcantonio JM, Tomlinson J (1991) Lens Calcium and Cataract. In: Obrecht G, Stark LW, eds. *Presbyopia Research*. New York: Plenum Press, 33-39.

Durrie DS (2006) The effect of different monovision contact lens powers on the visual function of emmetropic presbyopic patients (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc.* 104, 366–401.

Edwards KH, Gibson GA (2010) Intraocular lens short wavelength filtering. *Clin Exp Optom.* 93:6, 390-399.

Elliot DB (1987) Contrast sensitivity decline with ageing: a neural or optical phenomenon? *Ophthal Physiol Opt*. 7, 415-419.

Elliott DB (1993) Evaluating visual function in cataract. *Optom & Vis Sci*. 70(11), 896-902.

Empire Eye and Laser Center in Bakersfield, California: Aspheric IOLs Empireeyeandlaser.com (n.d.) [online image] Available at: http://empireeyeandlaser.com/monofocallens.html [Accessed: 29 Sep 2012].

Eppig T, Scholz K, Löffler A, et al (2009) Effect of decentration and tilt on the image quality of aspheric lens designs in a model eye. *J Cataract Refract Surg.* 35, 1091-1100.

Eyedesignbook.com (n.d.) [online image] Available at: http://www.eyedesignbook.com/ch3/fig3-59cBG.jpg [Accessed: 23 Oct 2012].

Eyedesignbook.com (n.d.) [online image] Available at: http://www.eyedesignbook.com/ch3/fig3-59aBG.jpg [Accessed: 23 Oct 2012].

Eye Health Problems and Eye Health Care Features from Optician Online - VRICS CET: C15989 Cataract - part 5 Opticianonline.net (2011) *Eye Health Problems and Eye Health Care Features from Optician Online - VRICS CET: C15989 Cataract - part 5*. [online image] Available at: http://www.opticianonline.net/Articles/2011/03/02/27225/VRICS+CET+C15989+Cataract+-+part+5.htm [Accessed: 11 Nov 2012].

Fahle M (2009) Perceptual learning and sensomotor flexibility: cortical plasticity under attentional control? *Philos Trans R Soc Land B Biol Sci.* 364, 313–19.

Fan KW (2005) Couching for cataract and Sino-Indian medical exchange from the sixth to the twelfth century AD. *Clin Exp Ophthal*. 33, 188-190.

Fatma N, Kubo E, Chylack LT Jr, Shinohara T, Akagi Y, Singh DP (2004) LEDGF regulation of alcohol and aldehyde dehydrogenases in lens epithelial cells: Stimulation of retinoic acid production and protection from ethanol toxicity. *Am J Physiol Cell Physiol.* 287, C508-C516.

Fernández-Vega L, Alfonso JF, Begoña Baamonde M, and Montés-Micó R (2007) Symmetric bilateral implantation of a distance-dominant diffractive bifocal intraocular lens. *J Cataract Refract Surg*. 33, 1913-1917.

Ferrer-Blasco T, Montes-Mico R, Peixoto-de-Matos SC, Gonzalez-Meijome JM, Cervino A (2009) Prevalence of corneal astigmatism before cataract surgery. *J Cataract Refract Surg*. 35, 70-75.

Fincham EF (1937) The Mechanism of Accommodation. *Br J Ophthalmol.* Suppl. 8, 5-80.

Finkelman YM, Ng JQ, Barrett GD (2009) Patient satisfaction and visual function after pseudophakic monovision. *J Cataract Refract Surg.* 35, 998–1002.

Fisher RF (1969) Elastic constants of the human lens capsule. *J Physiol.* 201:1, 1-19.

Fisher RF (1971) Elastic constants of the human lens. *J Physiol.* 212:1, 147-180.

Fisher RF (1977) The force of contraction of human ciliary muscle during accommodation. *Journal of Physiology.* 270- 251.

Fisher RF, Pettet BE (1973) Presbyopia and the water content of the human crystalline lens with age. *J Physiol.* 234:2, 443-447.

Fitch RC (1971) Procedural effects on the manifest human amplitude of accommodation. *Am J Optom Arch Am Acad Optom.* 48, 918-926.

Foster A (2000) Journal of Community Eye Health. *Community Eye Health*.13:34, 17-19.

Freeman EE, Munoz B, Turano KA, West SK (2006) Dynamic measures of visual function and their relationship to self-report of visual functioning. *Invest Ophthalmol Vis Sci .* 47, 4762-4766.

Gallagher SP, Pavilack MA (1999) Risk factors for anterior capsule contraction syndrome with polypropylene or poly(methylacrylate) haptics. *J Cataract Refract Surg.* 25, 1356-1361.

Gatinel D, Pagnoulle C, Houbrechts, Gobin L (2011) Design and qualification of a diffractive trifocal optical profile for intraocular lenses. *J Cataract Refract Surg.* 37, 2060-2067.

Gibbens MV, Goel R, smith SE (1989) Effect of cataract extraction on the pupil response to mydriatics. *Br J Ophthalmol.* 73, 563-565.

Gills JP, Van Der Karr M, Cherchio M (2002) Combined toric intraocular lens implantation and relaxing incisions to reduce high preexisting astigmatism. *J Cataract Refract Surg* 28. 1585- 1588.

Gilmartin B (1995) The aetiology of presbyopia: a summary of the role of lenticular and extralenticular structures. *Ophthal Physiol Opt.* 15:5, 431-437.

Glasser A (2008) Restoration of accommodation: surgical options for correction of presbyopia. *Clin Exp Optom.* 91:3, 279–295.

Glasser A, Campbell CW (1998) Presbyopia and the optical changes in the human crystalline lens with age. *Vision Res.* 38:2, 209-229.

Glasser A, Campbell MC (1999) Biometric, optical and physical changes in the isolated human crystalline lens with age in relation to presbyopia. *Vision Research.* 39:11, 1991-2015.

Glasser A, Campbell MC (1999) On the potential causes of presbyopia (reply). *Vision Res.* 39, 1267-1272.

Glasser A, Kaufman PL (1999) The mechanism of accommodation in primates. *Ophthalmology*. 106:5, 863-872.

Goes FJ (2008) Visual results following implantation of a refractive multifocal IOL in one eye and a diffractive multifocal IOL in the contralateral eye. *J Refract Surg.* 24, 300–305.

Goldmann H (1964) Senile changes of the lens and the vitreous. The Arthur J. Bedell Lecture. *Am J Ophthalmol.* 57, 1-13.

Greenbaum S (2002) Monovision Pseudophakia. *J Cataract Refract Surg.* 28, 1439–1443.

Grosvenor TP (1989) Primary Care Optometry, 2nd ed. New York, USA. Professional Press, 148-149.

Guirao A, Tejedor J, Artal P (2004) Corneal aberrations before and after small-incision cataract surgery. *Invest Ophthalmol Vis Sci.* 45, 4312-4319.

Gullstrand A (1911) How I Found the Intracapsular Mechanism of accommodation. *Nobel Lecture*, *11 December.*

Gunenc U, Celik L (2008) Long-term experience with mixing and matching refractive array and diffractive CeeOn multifocal intraocular lenses. *J Refract Surg.* 24, 233-242

Gupta N, Naroo SA, Wolffsohn JS (2007) Is randomisation necessary for measuring defocus curves in pre-presbyopes? *Contact Lens & Anterior Eye.* 30, 119-124.

Gupta N, Wolffsohn JSW, Naroo SA (2008) Optimizing Measurement of Subjective Amplitude of Accommodation with Defocus Curves. *J Cataract Refract Surg.* 34, 1329-1338.

Gur S, Ron S, Heicklen-Klein A (1994) Objective evaluation of visual fatigue in VDU workers. *Occup Med.* 44, 201-204.

Hahn GA, Penka D, Gehrlich C, Messias A, Weismann M, Hyvärinen L, Leinonen M, Freely M, Rubin G, Dauxerre C, Vital-Durand F, Featherston S, Dietz K,

Ham WT Jr, Ruffolo JJ Jr, Mueller HA, Guerry III D (1980) The nature of retinal radiation damage: dependence on wavelength, power level and exposure time. *Vision Res.* 20, 1105–11.

Hamasaki D, Ong J, Marg E (1956) The Amplitude of Accommodation in Presbyopia. *American Journal of Optometry & Archives of American Academy of Optometry*. 33:1, 3-14.

Hammond C (2001) The Epidemiology of Cataract. *Optometry Today.* 24-29.Handa T, Mukano K, Uoazato H, Niida T, Shoji N, Minei R, Nitta M, Shimzu K (2004) Ocular dominance and patient satisfaction after monovision induced by intraocular lens implantation. *J Cataract Refract Surg.* 30, 769–74.

Hankinson SE, Willett WC, Colditz GA, JM Seddon, Rosner B, Speizer FE, Stampfer MJ (1992) A prospective study of cigarette smoking and risk of cataract in women. *JAMA.* 268, 994-998.

Hansen SO, Tetz MR, Solomon KD, Borup MD, Brems RN, O'Morchoe DJ,

Bouhaddou O, Apple DJ (1988) Decentration of a flexible loop posterior chamber intraocular lenses in a series of 222 postmortem eyes. *Ophthalmology.* 95, 344-349.

Harding JJ (1993) Cigarette smoking and risk of cataract. *JAMA.* 269:6, 747-747.

Harding JJ (1995) Epidemiology, Pathophysiology and World Blindness. *Curr Opin Ophthalmol.* 6, 27-30.

Hawker MJ, Madge SN, Baddeley PA, and Perry SR (2005) Refractive expectations of patients having cataract surgery. *J Cataract Refract Surg*. 31, 1970-1975.

Hayashi K, Hayashi H (2006) Visual function in patients with yellow tinted intraocular lenses compared with vision in patients with non-tinted intraocular lenses. *Br J Ophthalmol.* 90, 1019-1023.

Hayashi K, Hayashi H, Oshika T, Hayashi F (2000) Fourier analysis of irregular astigmatism after implantation of 3 types of intraocular lenses. *J Cataract Refract Surg.* 26, 1510-1516.

Hayashi K, Manabe S, Yoshida M, Hayashi H (2010) Effect of astigmatism on visual acuity in eyes with a diffractive multifocal intraocular lens. *J Cataract Refract Surg.* 36, 1323–1329.

Hayashi K, Manabe S-I, Hayashi H (2009) Visual acuity from far to near and contrast sensitivity in eyes with a diffractive multifocal intraocular lens with a low addition power. *J Cataract Refract Surg.* 35, 2070-2076.

He JC, Gwiazda J, Thorn F, Held R (2003) Wave-front aberrations in the anterior corneal surface and the whole eye. *J Opt Soc Am A Opt Image Sci Vis.* 20, 1155–1163.

Heath GG (1956) The Influence of Visual Acuity on Accommodative Responses of the Eye. *Am J Optom Arch Am Acad Optom.* 33, 513-524.

Helmholtz HV (1855) Uber die Akkommodation des Auges. *A V Graefes Arch Klin Ophthalmol.* 1, 1-74.

Henderson BA, Grimes KJ (2010) Blue-blocking IOLs: a complete review of the literature. *Survey of Ophthalmology.* 55, 284-289.

Hengerer FH, Mellein AC, Buchner SE, Dick HB (2009) The light-adjustable lens – principles and clinical application. *Ophthalmoge.* 106, 260–264.

Hermans EA, Dubbelman GL, van der Heijde, Heethaar RM (2008) Change in the accommodative force on the lens of the human eye with age. *Vis Res.* 48, 119-126.

Heys KR, Cram SL, Truscott RJ (2004) Massive increase in the stiffness of the human lens with age: the basis for presbyopia? *Mol Vis.* 10, 956-963.

Hickenbotham A, Roorda A, Steinmaus, Glasser A (2012) Meta-Analysis of Gender Differences in Presbyopia. *IOVS [In Press]*

Hightower K, McCreedy J (1997) The Role of Calcium in UVB-Induced Damage in Irradiated Ocular Lenses. *Photochemistry & Photobiology.* 65:1, 155-160.

Hiller R, Sperduto RD, Podgor MJ, Wilson PF, Ferris FL, Colton T, D'Agostino RB, Roseman MJ, Stockman ME, Milton RC (1997) Cigarette smoking and the risk of development of lens opacities: the Framingham Studies. *Arch Ophthalmol.* 115, 1113-1118.

Hoffer KJ (1980) Biometry of 7500 cataractous eyes. *Am J Ophthalmol.* 90, 360-368.

Hoffmann PC, Hütz W W (2010) Analysis of biometry and prevalence data for corneal astigmatism in 23,239 eyes. *J Cataract Refract Surg*, *36*, 1479–1485.

Hofman T, Zuberbuhler B, Cervino A, Montés-Micó R, Haefliger E (2009) Retinal straylight and complaint scores 18 months after implantation of the AcrySof monofocal and ReSTOR diffractive intraocular lenses. *J Refract Surg.* 25, 485-492.

Hofstetter HW (1944) A comparison of Duane's and Donder's tables of the amplitude of accommodation. *Am J Optom.* 21, 345-363.

Hofstetter HW (1949) The course of presbyopia in several South African ethnic groups. *Am J Arch Am Acad Optom.* 40:1, 3-13.

Hofstetter HW (1968) Further data on presbyopia in different ethnic groups. *Am J Optom Arch Am Acad Optom.* 45, 522-527.

Hogan MJ, Alvarado JA, Weddell JE (1971) Histology of the Human Eye. Philadelphia. WB Saunders. 644- 645.

Hokoda SC, Cuiffreda KJ (1982) Measurement of accommodative amplitude in amblyopia. *Ophthalmic Physiol Opt.* 2, 205-212.

Holden BA, Fricke TR, Ho SM, Wong R, Schlenther G, Cronje S, Burnett A, Papas E, Naidoo KS, Frick KD (2008) Global impairment due to uncorrected presbyopia. *Arch Ophthalmol.* 126:12, 1731-1739.

Holladay JT, Piers PA, Koranyi G, van der Mooren M, Norrby S (2002) A new intraocular lens design to reduce spherical aberration of pseudophakic eyes. *J Refract Surg.* 18, 683-691.

Horn JD (2007) Status of toric intraocular lenses. *Curr Opin Ophthalmol.* 18, 58-61.

Huggert A (1953) The appearance of the band of dysjunction of the lens in diabetes mellitus. *Am J Ophthalmol.* 31, 227-234.

Hunter H Jr, Shipp M (1997) A study of racial differences in age at onset and progression of presbyopia. *J Am Optom Assoc.* 68, 171-177.

Hutz WW, Bahner K, Rohrig B Hengerer F (2010) The combination of diffractive and refractive multifocal intraocular lenses to provide full visual function after cataract surgery. *Eur J Ophthalmol.* 20, 370–375.

Hütz WW, Eckhardt H, Röhrig, Grolmus R (2008) Intermediate vision and reading speed with Array, Tecnis and ReSTOR intraocular lenses. *J Refract Surg.* 24, 251-256.

Ide T, Negishi K, Yamaguchi T, Hara S, Toda I, Tsubota K (2012) New compact accommodometer to measure accommodation amplitude as a biomarker. *Asia Pac J Ophthalmol.* 1, 24-27.

Images1.hellotrade.com (n.d.) [online image] Available at: http://images1.hellotrade.com/data2/LO/TE/HTVENDOR-4204537/new-images-stories-bilder-footage-ls312-20u-20ls313-20gross-250x250.jpg [Accessed: 19 Nov 2012].

Ivanhoff A (1956) About the Spherical Aberration of the Eye. *J Opt Soc Am*. 46, 901-903.

Ivers RQ, Mitchell P, Cumming RG (2000) Visual function tests, eye disease and symptoms of visual disability: a population-based assessment. *Clin Exp Ophthalmol*. 28, 41-47.

Jacobi FK, Kammann J, Jacobi KW, Grosskopf U, and Walden K (1999) Bilateral implantation of asymmetrical diffractive multifocal intraocular lenses*. Arch Ophth*. 117, 17-23.

Jacobi PC, Dietlein TS, Luke C, Jacobi FK (2002) Multifocal intraocular lens implantation in prepresbyopic patients with unilateral cataract. *Ophthalmology.* 111:5, 680-686.

Jacques PF, Chylack LT Jr, Hankinson SE, Khu PM, Rogers G, Friend J, Tung W, Wolfe JK, Padhye N, Willett WC, Taylor A (2001) Long-term nutrient intake and early age-related nuclear lens opacities. *Arch Ophthalmol.* 119, 1009-1019.

Jacques PF, Chylack LT, Taylor A (1994) Relationships between natural antioxidants and cataract formation. In: Frei B, ed. *Natural Antioxidants in Human Health and Disease*. San Diego. Academic Press, 515-533.

Jacques PF, Taylor A, Hankinson SE, Willett WC, Mahnken B, Lee Y, Vaid K, Lahav M (1997) Long-term vitamin C supplement use and prevalence of early age-related lens opacities. *Am J Clin Nutr.* 66, 911-916.

Jain IS, Jain GC, Kaul RL, Dhir SP (1979) Cataractogenous effect of hair dyes. A clinical and experimental study. *Ann Ophthalmol.* 11, 1681-1686.

Jain IS, Ram J, Gupta A (1982) Early onset of presbyopia. *Am J Optom & Physiol Optics.* 59:12, 1002-1004.

Jaschinski-Kruza W (1987) Is the Resting State of Our Eyes a favourable Viewing Distance for VDU work? In: Knave B, Wideback PG, eds. *Work with Display Units 86.* Amsterdam: Elsevier. 526- 538.

Javitt JC and Steinert RF (2000) Cataract extraction with multifocal intraocular lens implantation; a multinational clinical trial evaluating clinical, functional, and quality-of-life outcomes. *Ophthalmology*. 107, 2040-2048.

Johnson (1976) Effects of luminance and stimulus distance on accommodation and visual resolution. *J Opt Soc Am.* 66:2, 138-142.

Johnson CA, Casson EJ (1995) Effects of luminance, contrast sensitivity, and blur on visual acuity. *Optom Vis Sci*. 72, 864-869.

Jung CK, Chung SK, Baek NH (2000) Decentration and Tilt: Silicone multifocal versus acrylic soft intraocular lenses. *J Cataract Surg.* 26, 582-585.

Kasper T, Buhren J, Kohnen T (2006) Intraindividual comparison of high-order aberrations after implantation of aspherical and spherical intraocular lenses as a function of pupil diameter. *J Cataract Refract Surg.* 32, 78-84.

Kempen JH, Mitchell P, Lee KE, Tielsch JM, Broman AT, Taylor HR, Ikram MK, Congdon NG, O'Colmain BJ (2004) Eye Diseases Prevalence Research Group. The prevalence of refractive errors among adults in the United States, Western Europe and Australia. *Arch Ophthalmol.* 122, 495-505.

Kershner RM (2003) Retinal image contrast and functional visual performance with aspheric, silicone, and acrylic intraocular lenses. *J Cataract Refract Surg.* 29, 1684-1694.

Kimura W, Kimura T, Sawada T, Taguchi H, Hirokane C, Ohte A, Hitani H (1996) Postoperative decentration of three-piece silicone intraocular lenses. *J Cataract Refract Surg.* 22, 1277-1280.

Kleiman NJ, Spector A (1993) DNA single strand breaks in human lens epithelial cells from patients with cataract. *Curr Eye Res.* 12, 423-431.

Klein BEK, Klein R, Lee KR (1998) Incidence of Age-Related Cataract: the Beaver Dam Eye Study. *Arch Ophthalmol.* 116, 219-225.

Klein BEK, Klein R, Moss SE (1985) Prevalence of cataracts in a population-based study of persons with diabetes mellitus. *Ophthalmology.* 92, 191-196.

Klein BEK, Moss SE, Klein R, Lee KE, Cruickshanks KJ (2003) Associations of visual function with physical outcomes and limitations 5 years later in an older population – The Beaver Dam eye study. *Ophthalmology*. 110:644-650.

Koeppl C, Findl O, Kriechbaum K, Drexler W (2005) Comparison of pilocarpine-induced and stimulus-driven accommodation in phakic eyes. *Exp Eye Res*. 80, 795–800.

Kohnen T, Derhartunian V (2007) Apodized diffractive optic – new concept in multifocal lens technology. *Ophthalmologe.* 104, 899-904.

Koretz JF, Cook CA, Kaufman PL (2001) Ageing of the human lens: changes in lens shape at zero-diopter accommodation, *J Opt Soc Am A Opt Image Sci Vis,* 18:2, 265-272.

Koretz JF, Handelman GH (1982) Model of the accommodative mechanism in the human eye. *Vis Res.* 22:8, 917-927.

Koretz JF, Handelman GH (1983) A model of accommodation in the young human eye: the effects of lens elastic anisotropy on the mechanism. *Vis Res.* 23:12, 1679-1686.

Koretz JF, Handelman GH (1988) How the human eye focuses. *Sci Am.* 259:1, 92-99.

Koretz JF, Kaufman PL, Neider MW, Goeckner PA (1989) Accommodation and presbyopia in the human eye- Aging of the anterior segment. *Vis Res.* 29, 1685-1682.

Korynta J, Bok J, Cendelin J (1994) Changes in Refraction Induced by Change in Intraocular Lens Position. *J Refract Corneal Surg.* 10, 556-564.

Korynta J, Bok J, Cendelin J, Michalova (1999) Computer modeling of visual impairment caused by intraocular lens misalignment. *J Cataract Refract Surg.* 25, 100-105.

Krag S, Andreassen TT (2003) Mechanical properties of the human lens capsule. *Prog Retin Eye Res.* 22:6, 749-767.

Krag S, Andreassen TT (2003) Mechanical properties of the human posterior lens capsule. *Invest Ophthalmol Vis Sci.* 44, 691-696.

Krag S, Olsen T, Andreassen TT (1997) Biomechanical characteristics of the human anterior lens capsule in relation to age. *Invest Ophthalmol Vis Sci.* 38:2, 357-363.

Krag S, Oslen T, Andreassen TT (1996) Elastic properties of the lens capsule in relation to accommodation and presbyopia [ARVO Abstract] *Invest Ophthalmol Vis Sci.* 37, 3, S163*,* Abstract nr 774.

Krag S, Thim K, Corydon L, Kyster B (1994) Biomechanical aspects of the anterior capsulotomy. *J Cataract Refract Surg.* 20, 410-416.

Kragha IK (1986) Amplitude of accommodation: Population and methodological differences. *Ophthalmic Physiol Opt.* 6, 75-80.

Kragha IKOK (1985) Bifocal adds in Nigeria. *Am J Optom & Physiol Optics.* 62:11, 781-785.

Kragha IKOK, Hofstetter HW (1986) Bifocal adds and environmental temperature. *Am J Optom & Physiol Optics.* 63:5, 372-375.

Krumholz DM, Portello JK, Rosenfield M, Rosenbaum JD (2006) A combination solution for routine pupillary dilation. *Optometry*. 77, 350-353.

Lahm D, Lee LK, Bettelheim FA (1985) Age dependence of freezable and non-freezable water content of normal human lenses. *Invest Ophthalmol Vis Sci.* 26:8, 1162-1165

Lane S (2006) The AcrySof Toric IOL's FDA Trial Results. *Cataract & Refract Surg Today*. 5, 66-68

Langenbucher A, Huber S, Nguyen NX, Seitz B, Gusek-Schneider GC, Kuchele M (2003a) Measurement of accommodation after implantation of an accommodating posterior chamber intraocular lens. *J Cataract Refract Surg*. 29, 677-685.

Langenbucher A, Huber S, Nguyen NX, Seitz B, Kuchele M (2003b) Theoretical and measured pseudophakic accommodation after implantation of a new accommodative posterior chamber intraocular lens. *Arch Ophthalmol*. 121, 1722-1727.

Langley RK, Mortimer CB, McCulloch C (1960) The experimental production of cataracts by exposure to heat and light. *Arch Ophthalmol.* 63, 473-488.

Laube T, Apel H, Koch H-R (2004) Ultraviolet radiation absorption of intraocular lenses. *Ophthalmology.* 111, 880-885.

Lerman S (1980) Human Ultraviolet Radiation Cataracts. *Ophthal Res.* 12, 303-314.

Leske CM, Wu S-Y, Nemesure B, Hennis A (2002) Barbados Eye Studies Group. *Ophthalmology.* 109, 1303-1836.

Leske MC, Wu SY, Nemesure B, Li X, Hennis A, Connell AM (2000) Incidence and progression of lens opacities in the Barbados Eye Studies. *Ophthalmology.* 107, 1267-1273.

Levine L (1976) Effective degree of mydriasis with phenylephrine and tropicamide. *Am J Optom & Physiol Optics*. 53:12, 774-785.

Leyland M and Zinicola E (2003) Multifocal versus monofocal intraocular lenses in cataract surgery; a systematice review. *Ophthalmology*. 110, 1789-1798.

Leyland M, Pringle E (2006) Multifocal versus monofocal intraocular lenses after cataract extraction. Cochrane Database Syst Rev; issue 3, art no. CD003169. DOI: 10.1002/14651858. CD003169. Pub2. Available at: http://www.cochrane.org/reviews/en/ab003169.html.

Liang J, Williams DR (1997) Aberrations and retinal image quality of the normal human eye. *J Opt Soc Am (A).* 14, 2873-2883.

Lindstrom RL (1990) The surgical correction of astigmatism: a clinician's perspective. *Refract Corneal Surg.* 6, 441-454.

Lindstrom RL, Agapitos PJ, Koch D (1994) Cataract Surgery and Astigmatic Keratotomy. *International Ophthalmology Clinics*. 34:2, 145-164. [Original Article: PDF Only]

Löfgren S, Micheal R, Söderberg (2012) Impact of iris pigment and pupil size in ultraviolet radiation cataract in rat. *Acta Ophthalmol.* 90, 44-48.

London R (1991) Amplitude of Accommodation. In: JB Eskeridge, JF Amos and JD Bartlett, eds. *Clinical Procedures in Optometry*. Philadelphia. Lippincott, 69-71.

Lopez-Gil N, Montes-Mico R (2007) New intraocular lens for achromatzing the human eye. *J Cataract Surg.* 33, 1296-1302.

Lotery A, Xu X, Zlatava G, Loftus J (2007) Burden of illness, visual impairment and health resource utilisation of patients with neovascular age-related macular degeneration: results from the UK cohort of a five-country cross-sectional study. *Br J Ophthalmol.* 91, 1303-1307.

Lyle BJ, Mares-Perlman JA, Klein BE, Klein R, Gregor JL (1999) Antioxidant Intake and Risk of Incident Age-Related Nuclear Cataracts in the Beaver Dam Eye Study. *Am J Epidemiol.* 149, 801-809.

Madrid-Costa D, Cervino A, Ferrer-Blasco T, Garcia-Lazaro S, Montes-Mico R (2010) Visual and optical performance with hybrid multifocal intraocular lenses. Clin Exp Optom. 93:6, 426-440.

Mainster MA (1978) Spectral transmittance of intraocular lenses and retinal damage from intense light sources. *Am J Ophthalmol*. 85, 167–70.

Mainster MA (2006) Violet and blue blocking intraocular lenses: photoprotection versus photoreception. *Br J Ophthalmol.* 90, 784-792.

Mainster MA, Ham WT Jr, Delori FC (1983) Potential retinal hazards. Instrument and environmental light sources. *Ophthalmology.* 90, 927–32.

Mallen EA, Wolffsohn JS, Gilmartin B, Tsujimura (2001) Clinical Evaluation of the Shin-Nippon SRW-5000 Autorefractor in Adults. *Ophthal Physiol Opt*. 21:2, 101-107.

Mamalis N, Davis B, Nilson CD, Hickman MS, LeBoyer RM (2004) Complications of foldable intraocular lenses requiring explantation or secondary intervention-2003 survey update. *J Cataract Refract Surg.* 30, 2209-2218.

Manns F, Patel J-M, Denham D, et al. (2007) Optomechanical response of human and monkey lenses in a lens stretcher, *Invest Ophthalmol & Vis Sci.* 48, 3260-3268.

Manson JE, Christen WG, Seddon JM, Glynn RJ, Hennekens CH (1994) A prospective study of alcohol consumption and risk of cataract. *Am J Prev Med.* 10, 156-161.

Marcos S, Barbero S, Jimenez-Alfaro I (2005) Optical quality and depth-of-field of eyes implanted with spherical and aspheric intraocular lenses. *J Refract Surg.* 21, 223–35.

Mason HS, Ingram DJE, Allen B (1960) The free radical property of Melanins. *Arch Biochem Biophys.* 86, 225-230.

Mathews S (1999) Scleral expansion surgery does not restore accommodation in human presbyopia. *Ophthalmology*. 106, 873-877.

Maxwell WA, Lane SS, Zhou F (2009) Performance of presbyopia-correcting intraocular lenses in distance optical bench tests. *J Cataract Refract Surg.* 35, 166-171.

McCarty CA, Mukesh BN, Fu CL, Taylor HR (1999) The epidemiology of cataract in Australia. *Am J Ophthalmol.* 128, 446-465.

McGreggor LN, Chaparro A (2005) Visual difficulties reported by low-vision and nonimpaired older adult drivers. *Human Factors*. 47:469-478.

McKelvie J, McArdle B, McGhee (2011) The Influence of Tilt, Decentration, and Pupil Size on the Higher-Order Aberration Profile of Aspheric Intraocular Lenses. *Ophthalmology.* 118, 1724-1731

McKelvie J, McArdle B, McGhee (2011) Wavefront Aberrometry: Comparing and Profiling Higher-Order Aberrations Produced by Intraocular Lenses in vitro using a Physical Model Eye System and Hartman-Shack Aberrometry. *J Cataract Refract Surg.* 35, 547-555.

McLellan JS, Marcos S, Burns SA (2001) Age-Related Changes in Monochromatic Wave Aberrations of the Human Eye. *Invest Ophthalmol Vis Sci.* 42, 1390-1395.

McLeod SD, Portney V, Ting A (2003) A dual optic accommodating foldable intraocular lens. *Br J Ophthalmol.* 87, 1083–1085.

Mcleod SD, Vargas LG, Portney V, et al (2007) Synchrony dual-optic accommodating intraocular lens - Part 1: Optical and biomechanical principles and design considerations. *J Cataract Refract Surg*. 33:1, 37-46.

Mehr EB, Freid AN (1976) The measurement and recording of vision at near test distances. *Am J Optom Physiol Opt.* 53, 314–17.

Melki SA, Harissi-Dagher M (2011) Coaxially Sighted Intraocular Lens Light Reflex for centration of the multifocal single piece intraocular lens. *Can J Ophthalmol.* 46:4, 319-321.

Menapace R, Findl O, Kriechbaum K, Leydolt-Koeppl Ch (2007) Accommodating intraocular lenses: a critical review of present and future concepts. *Graefes Arch Clin Exp Ophthalmol.* 245, 473–89.

Mendicute J, Irigoyen C, Aramberri J, Ondarra A, Montés-Micó R (2008) Foldable toric intraocular lens for astigmatism correction in cataract patients. *J Cataract Refract Surg.* 34, 601-607.

Mendicute J, Irigoyen C, Ruiz M, Illarramendi I, Ferrer-Blasco T, Montés-Micó R (2009) Toric intraocular lens versus opposite clear corneal incisions to correct astigmatism in eyes having cataract surgery. *J Cataract Refract Surg*. 35, 451–458.

Mester U, Dillinger P, Anterist N (2003) Impact of a modified optic design on visual function: clinical comparative study. *J Cataract Refract Surg.* 29, 652–660.

Millidot M, Millidot S (1989) Presbyopia correction and the accommodation in reserve. *Ophthalmic Physiol Opt.* 9, 126-132.

Miranda (1979) The Geographic Onset in the Onset of Presbyopia. *Trans Am Ophthalmol Soc.* 77, 603-621.

Miranda (1980) Environmental Temperature and Senile Cataract. *Trans Am Ophthalmol Soc.* 78, 254-264.

Miyajima H, Katsumi O, Wang GJ (1992) Contrast visual acuities in cataract patients.I. Comparison with normal subjects. *Acta Ophthalmol* (Copenh). 70 (1), 44-52.

Monestam E, Lundqvist B (2006) Long-time results and associations between subjective visual difficulties with car driving and objective visual function 5 years after cataract surgery. *J Cat Refract Surg*. 32, 50-55.

Montés-Micó R, Alio JL (2003) Distance and Near Contrast sensitivity after multifocal intraocular lens implantation. *J Cataract Refract Surg.* 29, 703-711.

Montés-Micó R, Charman WN (2001) Choice of Spatial frequency for contrast sensitivity evaluation after corneal refractive surgery. *J Refract Surg.* 17, 646-651.

Montés-Micó R, Espana E, Bueno I, Charman WN, Menezo JL (2004) Visual performance with multifocal intraocular lenses: Mesopic contrast sensitivity under distance and near conditions. *Ophthalomology.* 111, 85-96.

Montés-Micó R, Ferrer-Blasco T, Cerviño A (2009) Analysis of the possible benefits of aspheric intraocular lenses: review of the literature. *J Cataract Refract Surg.* 35, 172–81.

Morgan PB, Efron N (2009) Prescribing soft contact lenses for astigmatism. *Contact Lens Ant Eye*. 32, 97-98.

Morny FK (1995) Correlation between Presbyopia, Age and Number of Births of Mothers in the Kumasi Area of Ghana. *Ophthalmic Physiol Opt.* 15:5, 463-466.

Mosad SM, Ghanem AA, El-Fallal HM, El-Kannishy AM, El Baiomy AA, Al-Diasty Am, Arafa LF (2010) Lens Cadium, Lead and Serum Vitamins C, E and Beta Carotene in Cataractous Smoking Patients. *Curr Eye Res.* 35:1, 23-30.

Moss SE, Klein R, Klein BEK (1987) Accommodative Ability in Younger-Onset Diabetes. *Arch Ophthalmol.* 105, 508-512.

Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA (2006) Development of Cataract & Associated Risk Factors. *Arch Ophthalmol.* 124, 79-85.

Muñoz G, Albarrán-Diego C, Ferrer-Blasco T, Sakla HF, and García-Lázaro S (2011) Visual function after bilateral implantation of a new zonal refractive aspheric multifocal intraocular lens. *J Cataract Refract Surg.* 37, 2043-2052.

Mutlu FM, Erdurman C, Sobaci G, Bayraktar MZ (2005) Comparisons of tilt and decentration of 1-piece and 3-piece hydrophobic acrylic intraocular lenses. *J Cataract Refract Surg.* 31, 343-347.

Mivision.com.au (n.d.) [online image] Available at: http://www.mivision.com.au/media/pics/site/imagecache/419BA2CFB776F0FD3476BB1FE67B7688.jpg [Accessed: 20 Nov 2012].

Nakazawa M, Ohtsuki K (1983) Apparent accommodation in pseudophakic eyes after implantation of posterior chamber intraocular lenses. *Am J Ophthalmol.* 96, 435–438.

Nakazawa M, Ohtsuki K (1984) Apparent accommodation in pseudophakic eyes after implantation of posterior chamber intraocular lenses – optical analysis. *Invest Ophthalmol Vis Sci.* 25, 1458–1460.

Nanavaty MA, Spalton DJ, Boyce J, Saha S, Marshall J (2009) Wavefront aberrations, depth of focus, and contrast sensitivity with aspheric and spherical intraocular lenses: fellow-eye study. *J Cataract Refract Surg.* 35, 663–671.

Nanavaty MA, Vasavada AR, Patel AS, Raj SM, Desai TH (2006) Analysis of patients with good uncorrected distance and near vision after monofocal intraocular lens implantation. *J Cataract Refract Surg.* 32, 1091–1097.

National Institute of Clinical Excellence (2004) Clinical practice guideline for the assessment and prevention of falls in older people. *Clinical Practice Guidelines.* 1-95.

Newsome DA (1989) Noninfectious ocular complications of AIDS. *Int Ophthalmol Clin.* 29, 95-97.

Nio YK, Jansonius NM, Fidler V, Geraghty E, Norrby S, Kooijman AC (2000) Age-related changes of defocus-specific contrast sensitivity in healthy subjects. *Ophthalmic Physiol Opt.* 20, 323-334.

Nio YK, Jansonius NM, Fidler V, Geraghty E, Norrby S, Koojiman AC (2002) spherical and irregular aberration are important for the optimal performance of the human eye. *Ophthalmic Physiol Opt.* 22, 103-112.

Nirmalan PK, Krishnaiah S, Shamanna BR, Rao GN, Thomas R (2006) A population-based assessment of presbyopia in the state of Andhra Pradesh, South India: The Andhra Pradesh Eye Disease Study. *Invest Ophthalmol Vis Sci.* 47, 2324-2328.

Nishi Y, Mireskandari K, Khaw P, Findl O (2009) Lens refilling to restore accommodation. *J Cataract Refract Surg.* 35, 374–382.

Novis C (2000) Astigmatism and Toric Intraocular Lenses. *Curr Opin Ophthalmol.* 11, 47-50.

Nwosu (1998) Ocular Problems of Young Adults in Rural Nigeria. *Int Ophthalmol.* 22, 259-263

Ohmi S, Uenoyama K (1995) Decentration associated with asymmetric capsular shrinkage and intraocular lens design in a rabbit model. *J Cataract Refract Surg.* 21, 293-296.

Olurin O (1973) Refractive errors in Nigerians: A hospital clinical study. *Ann Ophthalmol.* 5, 971-976.

Ong J (1981) Southeastern Asian Refugees' Presbyopia. *Percept Mot Skills.* 53:2, 667-670.

Ophthalmology Times Europe - Torsional ultrasound
Oteurope.com (n.d.) [online image] Available at:
http://www.oteurope.com/ophthalmologytimeseurope/content/printContentPopup.jsp?id=331090 [Accessed: 20 Nov 2012].

Orme ME, Paine AC, Teale CW, Kennedy LM (2002) Cost-effectiveness of the AMO Array multifocal intraocular lens in cataract surgery. *J Refract Surg.* 18, 162-168

Ossma IL, Galvis A, Vargas LG, Trager MJ, Vaqefi MR, McLeod SD (2007) Synchrony dual-optic accommodating intraocular lens. Part 2: pilot clinical evaluation. *J Cataract Refract Surg.* 33, 47-52.

Ostrin LA, Glasser LA (2004) Accommodation measurements in a prepresbyopic and presbyopic population. *J Cataract Refract Surg*. 30, 1435-1444.

Owens DA, Tyrrell RA (1999) Effects of luminance, blur, and age on nighttime visual guidance: A test of the selective degradation hypothesis. *J Exp Psychology-Applied*. 5:115-128.

Packer M, Fine H, Hoffman RS, Piers PA (2002) Prospective randomized trial of an anterior surface modified prolate intraocular lens. *J Refract Surg.* 18, 692–696.

Pager CK (2004) Expectations and outcomes in cataract surgery; a prospective test of 2 models of satisfaction. *Arch Ophth*. 122, 1788-1792.

Pande M, Hillman JS (1993) Optical zone centration in keratorefractive surgery: Entrance Pupil Center, Visual Axis, Coaxially Sighted Corneal Reflex or Geometric Corneal Centre? *Ophthalmology*. 100, 1230-1237.

Pärssinen O, Räty J, Vainikainen J, Timonen J, Lyyra AL (1998) Compression forces of haptics of freely rotating posterior chamber intraocular lenses. *J Cataract Refract Surg*. 24, 415-425.

Patel JI (2007) Is cataract surgery a risk factor for progression of macular degeneration? *Curr Opin Ophthalmol.* 18, 9-12.

Pedrigi RM, David G, Dzieayc J, Humphrey JD (2007) Regional mechanical properties and stress analysis of the human anterior lens capsule. *Vis Res.* 47, 1781-1789.

Pepose JS, Applegate RA (2005) Making sense out of wavefront sensing. *Am J Ophthalmol.* 139, 335-343.

Pepose JS, Qazi MA, Davies J, Doane JF, Loden JC, Sivalingham V, Mahmoud AM (2007) Visual performance of patients with bilateral vs combination Crystalens, ReZoom and ReSTOR intraocular lens implants. *Am J Ophthalmol.* 144, 347-357.

Pepose JS, Qazi MA, Edwards KH, Sanderson JP, Sarver EJ (2009) Comparison of contrast sensitivity, depth of field and ocular wavefront aberrationsin eyes with an IOL with zero versus positive spherical aberration. *Graefes Arch Clin Exp Ophthal.* 247:7, 965-973.

Petermeier K, Szurman P (2007) Subjective and objective outcome following implantation of the apodized diffractive AcrySof ReSTOR. *Ophthalmology.* 104:5, 399- 404, 406- 408.

Pieh S, Fiala W, Malz A, Stork W (2009) In vitro strehl ratios with spherical, aberration-free, average and customized spherical aberration-correcting intraocular lenses. *Invest Ophthalmol Vis Sci.* 50, 1264-1270.

Pieh S, Weghaupt H, and Skorpik C (1998) Contrast sensitivity and glare disability with diffractive and refractive multifical intraocular lenses*. J Cataract Refract Surg*. 24, 659-662.

Pierro L, Brancato R, Zaganelli E, Guarisco L, Calori G (1996) Correlation of lens thickness with blood glucose control in diabetes mellitus. *Acta Ophthalmol Scand.* 74, 539-541.

Pierscionek BK (1993) In vitro alteration of human lens curvatures by radial stretching. *Exp Eyes Res.* 5:5, 629-635.

Pierscionek BK (1995) Age-related response of human lenses to stretching forces. *Exp Eyes Res* 60:3, 325-332.

Pineda-Fernandez A, Jaramillo J, Celis V, et al. (2004) Refractive outcomes after bilateral multifocal intraocular lens implantation. *J Cataract Refract Surg.* 30, 685-688.

Pipe DM, Rapley LJ (1987) Ocular Anatomy and Histology. London: The Association of Dispensing Opticians. 109-112.

Pointer JS (1995) The Presbyopia Add, II. Age related trend and a gender difference. *Ophthalmic Physiol Opt.* 15, 241-248.

Pomerance GN and Evans DW (1994) Test-retest reliability of the CSV-1000 contrast test and its relationship to glaucoma therapy*. Invest Ophthalmol Vis Sci*. 35, 3357-3361.

Poyer JF, Kaufman PL , Flügel C (1993) Age does not affect contractile responses of the isolated rhesus monkey ciliary muscle to muscarinic agonists. *Curr Eye Res.* 12, 413-422.

Ramakrishnan S, Sulochana T, Abdul Rahim A (1995) Smoking of beedies and cataract: cadium and vitamin C in the lens and blood. *Br J Ophthalmol.* 79, 202-206.

Rambo CV (1953) Further notes on the varying ages at which different peoples develop presbyopia. *Am J Ophthalmol*. 36, 709-710.

Reddan JR, Dziedzic DC (1982) Insulin-Like Growth Fcators, IGF-1, IGF-2 and Somatomedin C trigger cell proliferation in mammalian epithelial cells cultured in a serum-free medium. *Exp Cell Res.* 142, 292-300.

Reddan JR, Wilson-Dziedzic D (1983) Insulin growth factor and epidermal growth trigger mitosis in lenses cultured in a serum-free medium. *Invest Ophthalmo Vis Sci.* 24, 409-416.

Remington LA (2005) Clinical Anatomy of the Visual System, Elsevier, Butterworth-Heinemann, 87, St Louis, Missouri.

Review of Ophthalmology® Moving Forward with the Crystalens Revophth.com (2012) [online image] Available at: http://www.revophth.com/content/d/features/i/1335/c/25605/ [Accessed: 20 Nov 2012].

Reznick AZ, Cross CE, Hu M (1992) Modification of plasma proteins by cigarette smoke as measured by protein carbonyl formation. *Biochem J.* 286, 607-611.

Richter-Mueksch S, Weghaupt H, Skorpik C, Velikay-Parel M, Radner W (2002) Reading performance with a refractive multifocal and a diffractive bifocal intraocular lens. *J Cataract Refract Surg.* 28, 1957-1963.

Roberts (2011) Ultravoilet radiation as a risk factor for cataract and macular degeneration. *Eye & Contact Lens.* 37, 246-249.

Rocha KM, Soriano ES, Chamon W, Chalita MR, Nose W (2007) Spherical aberration and depth of focus in eyes implanted with aspheric and spherical intraocular lenses: a prospective randomized study. *Ophthalmology.* 114, 2050-2054.

Rosenfield & Cohen (1996) Repeatability of clinical measurement of the amplitude of accommodation. *Ophthal Physiol Opt.* 16:3, 247-249.

Rosenfield M, Ciuffreda KJ (1991) Effect of surround propinquity on the open-loop accommodative response. *Invest Ophthalmol & Vis Sci.* 32:1, 142-147.

Rosenfield M, Cohen AS (1995) Push-up amplitude of accommodation and target size. *Ophthal Physiol Opt.* 15, 231-232.

Ruíz-Mesa R, Carrasco-Sanchez D, Diaz-Álvarez SB, Ruíz-Mateos MA, Ferrer-Blasco T, Montés-Micó R (2009) Refractive lens exchange with foldable toric intraocular lens. *Am L Ophthalmol.* 147, 990- 996, e1.

Rushwurm I, Scholz U, Zehetmayer M, Hanselmayer G, Vass C, Skorpik C (2000) Astigmatism correction with a foldable toric intraocular lens in cataracts patients. *J Cataract Surg.* 26, 1022-1027.

Rynders M, Lidkea B, Chisholm W, Thibos LN (1995) Statistical distribution of foveal transverse chromatic aberration, pupil centration and angle *ψ* in a population of young adult eyes. *J Opt Soc Am A.* 12:10, 2348-2357.

Sakai H, Hirata Y, Usui S (2007) Relationship between residual aberration and light-adapted pupil size. *Optom Vis Sci.* 84, 517-521.

Saw SM, Wong TY, Ting S, et al. (2007) The relationship between anterior chamber depth and the presence of diabetes in the Tanjong Pagar Survey. *Am J Ophthalmol.* 144, 325-326.

Schachar RA (1992) Cause and treatment of presbyopia with a method for increasing the amplitude of accommodation. *Ann Ophthalmol.* 24, 445-452.

Schachar RA (1994) Zonular Function: A new hypothesis with clinical implications. *Annals of Ophthalmology.* 26, 36-38.

Schachar RA (1995) The Mechanism of Ciliary Muscle Function. *Annals of Ophthalmology.* 27, 126-132.

Schachar RA (1999) Is Helmholtz Theory of accommodation correct? *Annals of Ophthalmology.* 31, 10-17.

Schacher RA, Tello C, Cudmore DP (1996) In vivo increase of the human lens equatorial diameter during accommodation. *Am J Physiol.* 271:3: Pt 2, R670-R676.

Schmidinger G, Simader C, Dejaco-Ruhswurm I, Skorpik C, and Pieh S (2005) Contrast sensitivity function in eyes with diffractive bifocal intraocular lenses. *J Cataract Refract Surg*. 31:11, 2076-2083.

Schwartz B (1965) Environmental temperature and the ocular temperature gradient. *Arch Ophthalmol.* 74, 237-243.

Schwiegerling J (2006) Blue-light-absorbing lenses and their effect on scotopic vision. *J Cataract Refract Surg.* 32, 141-144.

Sergienko NM, Kondratenko YN, Tutchenko NN (2008) Depth of focus in pseudophakic eyes. *Graefes Arch Clin Exp Ophthalmol.* 246, 1623-1627.

Shentu X, Tang X, Yao K (2008) Spherical aberration, visual performance and pseudoaccommodation of eyes implanted with different aspheric intraocular lens. *Clin Exp Ophthalmol.* 36, 620–624.

Sheppard A, Bashir A, Wolffsohn JS, Davies LN (2010) Accommodating intraocular lenses: a review of design concepts, usage and assessment methods. *Clin Exp Optom.* 93:6, 441-452.

Shimzu K, Misawa A, Suzuki Y (1994) Toric intraocular lenses: correcting astigmatism while controlling axis shift. *J Cataract Refract Surg.* 20, 523-526.

Shimzu K, Misawa A, Suzuki Y (1994) Toric intraocular lenses: correcting astigmatism while controlling axis shift. *J Cataract Refract Surg.* 20, 523-526.

Shirfar M (2008) Phakic intraocular lenses. *Curr Opin Ophthalmol.* 19, 349–356.

Siebinga I, Vrensen GF, De Mul FF, Greve J (1991) Age-related changes in local water and protein content of human eye lenses measured by Raman microspectroscopy. *Exp Eyes Res.* 53:2, 223-239.

Simpson MJ (1992) Diffractive multifocal intraocular lens image quality. *Applied Optics.* 31:19, 3621-3626.

Slataper FJ (1950) Age norms of refraction and vision. *Archives of Ophthalmology.* 43, 466-481.

Sliney DH (2001) Photoprotection of the eye- UV radiation and sunglasses. *J Photochem Photobiol B.* 64, 166-175.

Smith AB, Tanaka S, Halperin W (1984) Correlates of ocular and somatic symptoms among video display terminal users. *Hum Factors.* 26, 143-156.

Smith EM, Talamo JH (1995) Cyclotorsion in the seated and supine patient. *J Cataract Refract Surg.* 21, 402-403.

Smith EM, Talamo JH, Assil KK, Petaxhnick DE (1994) Comparison of astigmatic axis in the seated and supine positions. *J Cataract Refract Surg*. 10, 615-620.

Sparrow JM (2007) Cataract surgical rates: is there an overprovision in certain areas? *Br J Ophthalmol.* 91, 852–853.

Sparrow JM, Bron AJ, Brown NA, Neil HA (1990) Biometry of the crystalline lens in early-onset diabetes. *Br J Ophthalmol.* 74, 654-660.

Sparrow JM, Bron AJ, Phelps Brown NA, Neil HA (1992) Biometry of the crystalline lens in late-onset diabetes: The importance of diabetic type. *Br J Ophthalmol.* 76, 428-433.

Sparrow JR, Nakanishi K, Parish CA (2000) The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells. *Invest Ophthalmol Vis Sci.* 41, 1981–1989.

Spear PD (1993) Neural bases of visual deficits during aging*. Vis Res*. 33, 2589-2609.

Stachs O, Martin H, Kirchhoff A, Stave J, Terwee T, Guthoff R (2002) Monitoring accommodative ciliary muscle function using three-dimensional ultrasound. *Graefes Arch Clin Exp Ophthalmol.* 240, 906-912.

Steinert RF (2000) Visual outcomes with multifocal intraocular lenses. *Curr Opin Ophthalmol.* 11, 12-21

Steinert RF, Aker BL, Trentacost DJ, Smith PJ, Tarantino N (1999) A prospective comparative study of the AMO ARRAY zonal-progressive multifocal silicone intraocular lens and a monofocal intraocular lens. *Ophthalmology.* 106, 1243-1255.

Stevens MA, Bergmanson JPG (1989) Does sunlight cause premature aging of the crystalline lens. *J Am Optom Assoc*. 60:9, 660-663.

Strenk SA, Semmlow JL, Strenk LM, Munoz P, Gronlund-Jacob J, DeMarco JK (1999) Age-related changes in human ciliary muscle and lens: a magnetic resonance imaging study. *Invest Ophthalmol Vis Sci.* 40:6, 1162-1169.

Strenk SA, Strenk LM, Guo S (2006) Magnetic resonance imaging of aging, accommodating, phakic, and pseudophakic ciliary muscle diameters. *J Cataract Refract Surg.* 32, 1792–1798.

Strenk SA, Strenk LM, Koretz JF (2005) The mechanism of presbyopia. *Prog Ret Eye Res.* 24, 379-393.

Sun F, Stark L, Wong NJ, Nguyen A, Lakshminarayanan V, Mueller E (1988) Changes in accommodation with age: static and dynamic. *Am J Optom Physiol Opt.* 65, 492-498.

Sun X-Y, Vicary D, Montgomery P, Griffiths M (2000) Toric intraocular lenses for correcting astigmatism in 130 eyes. *Ophthalmology*. 107:9, 1776–1781; discussion by RM Kershner, 1781–1782.

Sun XY, Vicary D, Montgomery P, Griffiths M (2000) Toric intraocular lenses for correcting astigmatism in 130 eyes. *Ophthalmology* .107, 1776-1781.

Swanson GJ (1994) Diffractive trifocal intraocular lens design. Patent (US) No. 5344447

Taylor A, Jacques PF, Chylack Jr LT, Hankinson SE, Khu PM, Rogers G, Friend J, Tung W, Wolfe JK, Padhye N, Willett WC (2002) Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities. *Am J Clin Nutr.* 75, 540-549.

Taylor A, Jacques PF, Dorey DK (1993) Oxidation and aging: Impact on Vision. *Toxicol Ind Health.* 9, 349-371.

The Best of Ophthalmology EyeWorld News Magazine
Eyeworld.org (2012) [online image] Available at: http://www.eyeworld.org/article-early-cataract-detection-tool-developed [Accessed: 11 Nov 2012].

Thibos LN (1987) Calculation of the influence of lateral chromatic aberration on image quality across the visual field. *J Opt Soc Am A.* 4, 1673-1680.

Thornton S (1994) Astigmatic Keratotomy with Corneal Relaxing Incisions. *International Ophthalmology Clinics*. 34:4, 79-86. [Original Article: PDF Only]

Thornton SP (1990) Astigmatic keratotomy: A review of basic concepts with case reports. *J Cataract Refract Surg.* 16, 430-435.

Trauzettel-Klosinski S (2006) New standardised texts for assessing reading performance in four European languages. *Br J Ophthalmol*. 90, 480-484.

Tscherning M (1895) Recherches sur les changement optiques des l'ooeil pendent 'accommodation. *Arch de Physiol Norm et Pathol.* 7, 158-180.

Tscherning M (1909) H. v. Helmholtz et la theorie de l'accommodation, *Paris.*

Tucker J, Charman WN (1975) The depth-of-focus of the human eye for snellen letters. *Am J Optom Physiol Opt.* 52, 3-21.

Tucker J, Charman WN (1986) Depth of focus and accommodation for sinusoidal gratings as a function of luminance. *Am J Optom.* 63, 58-70.

Tyrell RA, Leibowitz HW (1990) The relation of vergence effort to reports of visual fatigue following prolonged near work. *Hum Factors.* 32, 341-357.

van Alphen GW, Graebel WP (1991) Elasticity of tissues involved in accommodation. *Vis Res.* 31, 1417-1438.

Van Den Berg TJTP (1995) Analysis of intraocular straylight, especially in relation to age. *Optom Vis Sci* . 72, 52-59.

Van Heyningen R, Harding JJ (1988) A case-control study of cataract in Oxfordshire: some risk factors. *Br J Ophthalmol.* 72, 804-808.

Vaquero-Ruano M, Encinas JL, Millan I, Hijos M, Cajigal C (1998) AMO Array multifocal versus monofocal intraocular lenses: long-term follow-up. *J Cataract Refract Surg.* 24, 118-123

Vision 2020. The cataract challenge. *Commun Eye Health.* 13, 17–19.

20-20visionperfection.co.uk (n.d.) [online image] Available at: http://www.20-20visionperfection.co.uk/files/5012/7859/9297/accomodating_iols_image.jpg [Accessed: 20 Nov 2012].

Vitale S, Ellwein L, Cotch MF, Ferris FL, Sperduto R (2008) Prevalence of refractive error in the United States, 1999-2004. *Arch Ophthalmol*.126:1111-1119.

Volume 1, Chapter 73B. Clinical Evaluation of Cataracts Oculist.net (1862) [online image] Available at: http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v1/v1c073b.html [Accessed: 11 Nov 2012].

Voskresenskaya A, Pozdeyeva N, Pashtaev N, Batcov Y, Treushnicov V, Cherednik V (2010) Initial results of trifocal diffractive IOL implantation. *Graefes Arch Clin Exp Ophthalmol.* 248, 1299-1306.

Wagstaff DF (1966) The objective measurement of the amplitude of accommodation- parts VI and VII. *Optician.* 151, 322-326, 431-436.

Walsh G (1988) The effect of mydriasis on the pupillary centration of the human eye. *Ophthalmic Physiol Opt*. 8:178-182.

Walsh G, Charman WN (1988) The effect of pupil centration and diameter on ocular performance. *Vis Res*. 28, 659-665.

Wang L, Koch DD (2005) Effect of decentration of wavefront-corrected intraocular lenses on the higher-order aberrations of the eye. *Arch Ophthalmol.* 123, 1226-1230

Wang Y, Zhao K, Jin Y, Niu Y, Zuo T (2003) Changes of higher order aberration with various pupil sizes in the myopic eye. *J Refract Surg.* 19, S270-S274.

Weale (1989) Presbyopia toward the end of the 20th century. *Surv Ophthalmol.* 34:1, 15-30.

Weale RA (2003) Epidemiology of refractive errors and presbyopia. *Surv Ophthalmol*, 48, 515-543.

Weale RA (1963) New light on old eyes. *Nature.* 198, 944-946.

Weale RA (1981a) Human ocular aging and ambient temperature. *Br J Ophthalmol.* 65, 869-870.

Weale RA (1981b) The Aging Eye: Geographic and Climatic influence on the aging process. *2nd Symposium International de la Presbytie. Paris: Essilor Press,* 177-179

Weeber HA, Eckert G, Pechhold W, van der Heijde RJL (2007) Stiffness gradient in the crystalline lens. *Graefe's Arch Clin Exp Ophthalmol*. 245, 1357-1366.

Weeber HA, Eckert G, Soergel F, Meyer CH, Pechhold W, van der Heijde RG(2005) Dynamic mechanical properties of human lenses. *Exp Eye Res.* 80, 425-434.

Weimer NG, Dubbleman M, Hermans EA, Ringens PJ, Polak BCP (2008a) Changes in the internal structure of the human crystalline lens with diabetes mellitus type 1 and type 2. *Ophthalmology.* 115, 2017-2023.

Weimer NG, Dubbleman M, Kostense PJ, Ringens PJ, Polak BC (2008b) The influence of diabetes mellitus type 1 and 2 on the thickness, shape and equivalent refractive index of the human crystalline lens. *Ophthalmology.* 115, 1679-1686.

Weiss JN, Nishio I, Clark JI, Tanaka T, Benedek GB, Giblin FJ, Reddy VN (1982) Early detection of cataractogenesis by laser light scattering. *Invest Ophthalmol Vis Sci (ARVO Suppl)*, 41.

Westcott MC, Ward M, Mitchell SM (2001) Failure of accommodation in patients with HIV infection. *Eye.* 15, 474-478.

Wilson MA, Campbell MCW, Simonet P (1992) Change of pupil centration with change of illumination and pupil size. *Optom Vis Sci*. 69, 129-136.

Wilson RS (1997) Does the lens diameter increase or decrease during accommodation? Human accommodation studies: a new technique using infrared retro-illumination video photography and pixel unit measurements, *Trans Am Ophthalmol Soc.* 95, 261-267 discussion 267-70.

Winn B, Whitaker D, Elliott DB, Phillips NJ (1994) Factors affecting light-adapted pupil size in normal human subjects. *Invest Ophthalmol Vis Sci*. 35, 1132-1137.

Winn-Hall DM, Glasser A (2008) Objective accommodation measurements in prepresbyopic eyes using an Autorefractor and an Aberrometer. *J Cataract Refract Surg.* 34, 774-784.

Wold JE, Hu A, Chen S, Glasser A (2003) Subjective and objective measurement of human accommodative amplitude. *J Cataract Refract Surg.* 29, 1878-1888.

Wolffsohn JS, Buckhurst PJ (2010) Objective Analysis of Toric Intraocular Lens Rotation and Centration. *J Cataract Refract Surg*. 36, 778-782.

Wolffsohn JS, Cochrane AL (1999) The changing face of the visually impaired. The Kooyong low vision clinic's past, present and future. *Optom Vis Sci*. 76, 747-754.

Wolffsohn JS, Cochrane AL (2000) Design of the low vision quality of life questionnaire (LVQOL) and measuring the outcome of low vision rehabilitation. *Am J Ophthalmol.* 130, 793-802.

Wolffsohn JS, Davies LN (2010) Intraocular lenses in the 21st century. *Clin Exp Optom*. 93:6, 377-378.

Wolffsohn JS, Davies LN, Gupta N, Naroo SA, Gibson GA, Mihashi T, Shah S (2010b) Investigating the mechanism of action of the Tetraflex KH3500 'accommodative' intraocular lens. *J Refract Surg*. 26:11, 858-862

Wolffsohn JS, Hunt OA, Gilmartin B (2002) Continuous measurement of accommodation in human factor applications. *Ophthal Physiol Opt.* 22, 380-384.

Wolffsohn JS, Hunt OA, Naroo SA, Gilmartin B, Shah S, Cunliffe IA, Benson MT, Mantry S (2006a) Objective accommodative amplitude and dynamics with the 1CU accommodative intraocular lens. *Invest Ophthalmol Vis Sci.* 47, 1230–1235.

Wolffsohn JS, Naroo SA, Motwani NK, Shah S, Hunt OA, Mantry S, Sira M, Cunliffe IA, Benson MT (2006b) Subjective and objective performance of the Lenstec KH-3500 'accommodative' intraocular lens. *Br J Ophthalmol.* 90, 693–696.

Wolffsohn JS, O'Donnell C, Charman WN, Gilmartin B (2004) Simultaneous continuous recording of accommodation and pupil size using the modified Shin-Nippon SRW-5000 Autorefractor. *Ophthal Physiol Opt.* 24, 142-147.

Wolffsohn JS, Sheppard AL, Vakani S, Davies LN (2011) Accommodative amplitude required for sustained near work. *Ophthalmic Physiol Opt*. 31, 480-486.

Woodward MA, Randleman B, Stulting D (2009) Dissatisfaction after multifocal intraocular lens implantation. *J Cataract Surg.* 35, 992-997.

Wyatt HJ (1995) The Form of the Human Pupil. *Vis Res*. 35, 2021-2036

Yang Y, Thompson K, Burns SA (2002) Pupil location under mesopic, photopic, pharmacologically dilated conditions. *Invest Ophthalmol Vis Sci*. 43, 2508-2512.

Yehezkel O, Belkin M, Sagi D, Polat U (2005) Adaptation to monocular astigmatic distortion is disrupted by conflicting binocular input. *Invest Ophthalmol Vis Sci.* 46:S5632 [Abstract].

Young RW (1992) Sunlight and age-related eye disease. *J Natl Med Assoc.* 84, 353-358.

Zadnik K (1997) The Ocular Examination: Measurements and Findings. 1st ed. Philadelphia: WB Saunders Company. 88-98.

Zeng J, Borchman D, Paterson CA (1998) Acute effect of ethanol on lens cation homeostasis. *Alcohol.* 16, 189-193.

Zhang F, Sugar A, Jacobsen G, and Collins MJ (2011) Visual function and spectacle independence after cataract surgery: Bilateral diffractive multifocal intraocular lenses versus monovision pseudophakia*. J Cataract Refract Surg*. 37, 853-858.

Zigman S, Schultz J, Yulo T (1973) Possible roles of near UV light in the cataractous process. *Exp Eye Res.* 15:2, 201-208.

Zigman S, Schultz JB, Yulo T, Grover D (1972) Effects of near-UV irradiation on lens and aqueous humor proteins. *Isr J Med Sci.* 8:8, 1590-1595.

Zigman S, Vaughan T (1979) Near ultraviolet light effects on the lenses and retinas of mice. *Invest Ophthalmol.* 13:6, 462-465.

Zigman S, Yulo T, Schultz J (1974) Cataract induction in mice exposed to near UV light. *Ophthal Res.* 6, 259-270.

APPENDIX

A1.

LIFESTYLE QUESTIONNAIRE

1. Age: ________

2. Gender: ☐ Male ☐ Female

3. What is your occupation?

____

4. How would you describe your ethnic group? The categories below were those used in the 2001 census and are recommended by the Commission for Racial Equality.

A White

☐ British

☐ Irish

☐ Other White background (please state) ______________________

B Mixed

☐ White and Black Caribbean

☐ White and Black African

☐ White and Asian

☐ Other Mixed background (please state) ______________________

C Asian or Asian British

☐ Indian

☐ Pakistani

☐ Bangladeshi

☐ Other Asian background (please state) ______________________

D Black or Black British

☐ Caribbean

☐ African

☐ Other Black background (please state) ______________________

E Chinese or other ethnic group

☐ Chinese

☐ Any Other (please state) ________________________________

5. Height: ________

6. a) Weight: ________

b) Has this been your approximate weight the past ten years?

☐ Yes ☐ No If no, how has it changed? ________

7. Iris colour: ☐ Black/dark brown ☐ Brown ☐ Light brown

☐ Hazel ☐ Green ☐ Grey

☐ Blue

☐ Other (please state, e.g. light brown/hazel) _____________

8. Do you smoke? ☐ Yes ☐ No

If yes, please go to question 9. If no, please go to question 10.

9. a) Approximately how many cigarettes do you smoke in a week? ___

b) What brand(s) of cigarette do you smoke most regularly?

____

c) How many years have you smoked for? ________

10. Have you ever been a regular smoker in the past? ☐ Yes ☐ No

If yes, please go to question 11. If no, please go to question 12.

11. a) Approximately how many cigarettes did you smoke in a week? __

b) What brand(s) of cigarette did you smoke most regularly?___________

c) How many years did you smoke for? ________

d) How long has it been since you stopped smoking? ________

12. a) Which of the following best describes your current dietary background?

☐ Meat eater ☐ Vegetarian ☐ Partly vegetarian ☐ Vegan

Please specify as appropriate, e.g. 'meat eater but no beef' or 'vegetarian but eat eggs' or 'partly vegetarian (eat fish)'.

____

(i) On average, how many servings of vegetable do you eat *per week*?

____

(ii) On average, how many servings of fruit do you eat *per week*?

____

(iii) On average, how many eggs (including yolks) do you eat *per week*?

____

(iv) a) On average, how many servings of oily fish do you eat *per week*?

____

b) Has this been your dietary background for the past ten years?

☐ Yes ☐ No If no, how has it changed? ________

13. a) Do you drink alcohol? ☐ Yes ☐ No

If yes, approximately how many units do you consume in a week? _____

1 alcopop bottle = 1.4 units.

1 bottle of average strength beer/lager/cider = 1.7 units.

1 can of average strength beer/lager/cider = 2.2 units.

1 pint (568 ml) of average strength beer/lager/cider = 2.8 units.

1 strong cocktail = 4 units.

25 ml spirit/shot = 1 unit (gin, rum, sambuca, tequila, vodka, whisky).

35 ml spirit/shot = 1.3 units.

1 bottle of average strength wine (12% vol) = 9 units.

1 small glass (125 ml) of wine = 1.5 units.

1 standard glass (175 ml) of wine = 2.1 units.

1 large glass (250 ml) of wine = 3 units.

b) Has this been your approximate alcohol consumption for the past ten years?

☐ Yes ☐ No If no, how has it changed? ________

14. a) Approximately how many daylight hours *per week* do you spend outdoors (i.e. outside of buildings/vehicles and therefore exposed to light) in:

Autumn/Winter months? ________ Spring/Summer months? ________

b) Has this been your approximate light exposure for the past ten years?

☐ Yes ☐ No If no, how has it changed? ________

15. Do you spend time abroad exposed to strong sunlight _____ weeks/year

16. a) Do you use sun beds or tanning booths regularly? ☐ Yes ☐ No

If yes, how often and for how long on average?

____

____

b) Has this been your habit for the past ten years?

☐ Yes ☐ No If no, how has it changed? ________

17. Is your skin particularly sensitive to sunlight? ☐ Yes ☐ No

18. a) In bright conditions, how often do you wear sunglasses?

☐ Always ☐ Most of the time ☐ Sometimes

☐ Occasionally ☐ Very rarely ☐ Never

b) Has this been your habit for the past ten years?

☐ Yes ☐ No If no, how has it changed? ________

19. a) Have you ever visited or lived in a country of hot climate?

☐ Yes ☐ No

b) if yes how much time have you spent abroad?

____

20. Do you or have you used hair dye?

☐ Yes ☐ No

If yes, when and for how long?

____

____

21. Have you had any kind of medical condition such as diabetes? ☐ Yes ☐ No

If yes, what and when was it diagnosed / treated?

____

____

22. Are you taking any medication?

☐ Yes ☐ No

If yes, what and what for and how long have you been taking the medication?

____

____

23. Have you taken any regular vitamins or supplements over the last 10 years?

☐ Yes ☐ No

If yes, what and for how long? (Please include as much detail as possible, e.g. Superboots Multivitamin A-Z, 1 tablet 3x/week and Seven Oceans 650mg fish oils, 1 cap/day)

____

____

____

24. Do you wear glasses? ☐ No ☐ Yes – which type do you wear? ____________

a) If you wear glasses for reading at what age did you start wearing them?___________

25. How much time do you spend wearing your glasses? ___________________

____

26. Do you wear contact lenses? ☐ No ☐ Yes – how much of the time and for how long? ______

27. a) Do you have any kind of eye condition, besides needing spectacles?

☐ Yes☐ No

If yes, what and when was it diagnosed/treated?

____

b) Are you taking any kind of medication for this eye condition?

____

28. Do you use a PC or laptop?

☐ Yes ☐ No

If yes, how many hours daily do you spend on it? _______________hrs

How far away is your screen _______________cm

29. Do you use a mobile phone?

☐ Yes ☐ No

If yes, how far away do you hold your mobile? __________________cm

30. How much time do you spend on reading or any other near tasks?

____

At what distance do you typically read?

___________________cm

If you have any further comments regarding your lifestyle, please write them here:

____

____

____

A2. THE NEAR ACTIVITY VISUAL QUESTIONNAIRE (NAVQ)

How much difficulty do you have:	N/A or stopped for non-visual reasons	No Difficulty	A little difficulty	Moderate difficulty	Extreme Difficulty
1. Reading small print, such as: newspaper articles, items on a menu, telephone directories?	x	0	1	2	3
2. Reading labels/ instructions/ ingredients/ prices such as on: medicine bottles, food packaging?	x	0	1	2	3
3. Reading your post/ mail, such as: electric bill, greeting cards, bank statements, letters from friends & family?	x	0	1	2	3
4. Writing and reading your own writing, such as: greeting cards, notes, letters, filling in forms, checks, signing your name?	x	0	1	2	3
5. Seeing the display & keyboard on a computer or calculator?	x	0	1	2	3
6. Seeing the display & keyboard on a mobile or fixed telephone?	x	0	1	2	3
7. Seeing objects close to you and engaging in your hobbies, such as: playing card games, gardening, seeing photographs?	x	0	1	2	3
8. Seeing objects close to you in poor or dim light?	x	0	1	2	3
9. Maintaining focus for prolonged near work?	x	0	1	2	3
10. Conducting near work without spectacles?	x	0	1	2	3

OVERALL	Completely Satisfied	Very Satisfied	Moderately Satisfied	A little satisfied	Completely Unsatisfied
How satisfied are you with your near vision?	0	1	2	3	4

A3. The Near Visual Activity Questionnaire (NAVQ) Linear Adjustment

The summated NAVQ score can be converted to a linear scale using the following table. Any ‘N/A’ responses are scored according to the median overall score for the subject

Non-Adjusted Score	Rasch Score	Non-Adjusted Score	Rasch Score
0	0	16	56.89
1	10.72	17	58.89
2	18.13	18	60.84
3	23.07	19	62.77
4	26.96	20	64.68
5	30.30	21	66.81
6	33.3	22	68.58
7	36.08	23	70.62
8	38.70	24	72.77
9	41.22	25	75.09
10	43.65	26	77.68
11	46.02	27	80.72
12	48.32	28	84.59
13	50.56	29	90.55
14	52.73	30	100
15	54.84		

A4. Amplitude of Accommodation & Presbyopia Onset Studies

Study/Author	Age Range (yrs) & Sample Size	Techniques Used	Countries Examined	Average Age of Presbyopia Onset (yrs)
Jain *et al.,* 1982	30-65 years 800 subjects	Minus lens technique at 33.3cm from clear to blur. Presbyopia determined as amplitude of accommodation below 3.75D	India	40
Miranda 1979	703 questionnaires	Questionnaire sent to 1,500 ophthalmologists throughout world	Norway Finland Alaska Canada Sweden Denmark N. USA Germany Ireland Holland Belgium Mid USA Puerto Rico India Malaysia Thailand	46.1 44.5 44.1 44.7 43.8 42.5 44 43.5 46.5 45.3 44.8 43.3 39.8 40 38.9 40.5*

Ayrshire 1964	30-75 years 1307 eyes	Push-up test using small print text	England	47
Turner 1958	18-62 years 5000 subjects	Push-up test using small print text Homatropine used on subjects <20years	England	43
Duane 1912	10-60 years 4200 subjects	Push-up test using thin lines as target. Homatropine used for subjects <48years	New York	45
Allen 1961	-	-	Cleveland	50
Kajiura 1965	1651 subjects	Push-test, defined presbyopia as amplitude of 3-4D	Japan	45
Fukuda 1965	-	-	Japan	43
Hamasaki 1956	42-60 years 106 subjects	Stigmatoscopy and push-up tests	California	43
Fitch 1971	13-67 years 110 subjects	Apparatus consisting of head rest and movable rod for advancing target. Target of 1mm used. No definition of presbyopia.	Texas	45
Coates 1955	10-80 years 4038 eyes	Exact methodology not stated but target size and illumination standardised	South Africa	40

Raphael 1961	35- 80 years 10,000 refractions	Amplitude measured using Lindsay optometer	Israel	41
Rambo & Sangal 1960	-	Push-up test with single line as target. Presbyopia defined as amplitude of accommodation of 3D	India	37
Miranda 1977 (cited in Miranda 1979)	1000 subjects Age-range not stated	Minus lens technique used. Presbyopia defined as amplitude of accommodation ≤3.75D	Puerto Rico	39
Burke *et al.,* 2006	40-65+ years 1562 subjects	Presbyopia defined as inability to read N8 at 40cm with distance correction and improvement with additional lens	Tanzania	61.7% at 40 yrs
Nirmalan *et al.,* 2006	30-102yrs 5587 subjects	Presbyopia defined as addition of at least +1.00D to give at least N8 near acuity	India	36.6 yrs in 30-39 yr age group

*small selection of data from study presented

A5. Power Calculations

A5.1. Sample Size for Chapter 2

No previous studies investigating the effects of astigmatism on daily tasks exist therefore sample sizes for glare testing and subjective rating could not be calculated. However, sample sizes for contrast sensitivity from previous studies (Dougherty *et al.,* 2008) with a sample size of 68, can be calculated. Statistical power of 80%, significance level of 0.05 with an effect size of 20cpd gives a minimum sample size of 14.

Previous studies of reading speed and near acuity (Chung *et al.,* 2007) quote a sample size of 19. Minimum sample size with 80% statistical power, significance level of 0.05 and effect size of 0.1 for near acuity and 10wpm for reading speed are calculated as 2 and 4 respectively.

A5.2. Sample Size for Chapter 3

Previous sample sizes of pupil centration studies vary from 8-70 subjects (Walsh 1988; Wilson *et al.,* 1992; Wyatt 1994; Yang *et al.,* 2002). Using data from Yang *et al.,* (2002) with statistical power size of 80% and significance level of 0.05 and meaningful difference of 0.1mm, the minimum sample size required is calculated as 10.

A5.3. Sample Size for Chapter 4

No recent studies have assessed changes in pupil size following cataract surgery therefore sample sizes using statistical power cannot be performed. A sample size of 25 patients was used in an early study by Gibbens *et al* (1989) but no standard deviations were reported. Kohnen *et al* (2003) however measure pupil sizes with a pupilometer amongst a sample of 50.

Minimum sample size for digital measurements of pupil dilation, with statistical power of 80% an effect size of 0.2mm, is calculated as 102.

A5.4. Sample Size for Chapter 5

Sample sizes for ethnicity range from 332 to 692 (Carnevali *et al.,* 2005; Edwards *et al.,* 1993; Hunter *et al.,* 1997) however as no standard deviations were reported in the above studies minimum sample sizes could not be calculated; also presbyopia onset was determined from additions prescribed and not measurement of amplitude of accommodation within these studies. Minimum sample sizes also could not be calculated for iris pigment, UV exposure, smoking and mobile phone usage as no pervious data exists in relation to accommodation. For VDU usage, Gur *et al* (1994) report sample sizes of 16 users and 13 controls however again no standard deviation values are reported thus minimum samples cannot be calculated.

For the following variables, statistical power of 80% and significance level of 0.05 was used to calculate sample sizes.

Minimum sample size for measuring accommodation amongst alcohol consumers and controls with effect size of 0.50 dioptres, using average data, was calculated as 152.

Minimum sample size calculated for measurement and comparison of amplitude of accommodation in diabetics and normals was calculated as 241.

A5.5. Sample Size for Chapter 6

To measure the appropriate sample size required for validation of a new accommodation measuring device, statistical power selected was 80%, significance level of 0.05 and an effect size of 1 dioptre. Sample sizes vary from 28 to 57 (Ostrin and Glasser 2004; Rutstein *et al.,* 1993), the minimum sample size was calculated using the averages of previous studies to give 37 patients.

A5.6. Sample Size for Chapter 7

Initial results of trifocal diffractive IOL implantation; Voskresenskaya *et al.,* 2010 reports a sample size of 36 patients. The sample sizes for the following measures were calculated using statistical power of 80% and significance of 0.05.

Minimum sample size for measurements of BCVA with a trifocal implant, with effect size of 0.1 is calculated as 42.

For CIVA at 50cm with an effect size of 0.1 a minimum sample size of 8 is required.

6-months postoperative assessments for trifocal implants minimum sample size is calculated as 11 with an effect size of 0.5.

A6. Additional References used in Appendix

Allen DG (1961) Accommodation after the age of forty years. *Am J Ophthal.* 52,702-705.

Ayrshire Study Circle (1964) An investigation into accommodation. *Br J Physiol Opt.* 21, 31-35.

Coates WR (1955) Amplitudes of accommodation in South Africa. *Br J Physiol Opt.* 12, 76-86.

Dougherty PJ, Waring G, Chavet A, Fischer J, Fant B, Bains HS (2008) Topographically guided laser in situ keratomileusis for myopia using a customized aspherical treatment zone. *J Cataract Refract Surg.* 34:11, 1862-1871.

Duane A (1912) Normal values of the amplitude of accommodation at all ages. *J Am Med Assoc. 59,* 1010-1013.

Fitch RC (1971) Procedural effects on the manifest human amplitude of accommodation. *Am J Optom.* 48, 918-926.

Fukuda M, Hamada Y, Marvo T (1962) Accommodation-age relation of Japanese. *Acta Ophthalmol Jpn.* 66, 181-188.

Kajiura M (1965) Studies on presbyopia. *Jpn J Ophthalmol*. 9,85-92.

Rambo VC, Sangal SP (1960) A study of the accommodation of the people of India. *Am J Ophthalmol.* 49,993-1004.

Raphael J (1961) Accommodational variations in Israel 1949-1960. *BrJ Physiol Opt*. 18, 181-185.

Turner MJ (1958) Observations on the normal subjective amplitude of accommodation. *Br J Physiol Opt.* 15, 70-100.

Chung STL, Jarvis SH, Cheung SH (2007) The effect of dioptric blur on reading performance. *Vis Res.* 47, 1584-1594.

Kohnen T, Terzi E, Bühren J, Kohnen EM (2003) Comparison of a digital and a handheld infrared pupillometer for determining scotopic pupil diameter. *J Cataract Refract Surg*. 29:1, 112-117.

Edwards MH, Law LF, Lee CM, Leung KM, Lui WO (1993) Clinical norms for amplitude of accommodation in Chinese. *Ophthal Physiol Opt.* 13, 199-204.

A7. Supporting Publications

Wolffsohn JS, Bhogal GK, Shah S (2011) Effect of Uncorrected Astigmatism on Vision. *J Cataract & Refract Surg*. 37:3, 454-460.

Bhogal,GK Wolffsohn,JS (2011) Intraocular lenses: a review of technological developments and the optometrist's role. *Optometry in Practice*. 12: 1-10