DOCTOR OF PHILOSOPHY

Anterior segment anomalies and effects on visual quality

Samantha McGinnigle

2013

Aston University

ANTERIOR SEGMENT ANOMALIES AND EFFECTS ON VISUAL QUALITY

SAMANTHA MCGINNIGLE

Doctor of Philosophy

ASTON UNIVERSITY

JULY 2013

ASTON UNIVERSITY

ANTERIOR SEGMENT ANOMALIES AND EFFECTS ON VISUAL QUALITY

SAMANTHA MCGINNIGLE
Doctor of Philosophy
JULY 2013

Summary

The tear film, cornea and lens dictate the refractive power of the eye and the retinal image quality is principally defined by diffraction, whole eye wavefront error, scatter, and chromatic aberration. Diffraction and wave aberration are fundamentally pupil diameter dependent; however scatter can be induced by refractive surgery and in the normal ageing eye becomes an increasingly important factor defining retinal image quality. The component of visual quality most affected by the tear film, refractive surgery and multifocal contact and intraocular lenses is the wave aberration of the eye. This body of work demonstrates the effects of each of these anomalies on the visual quality of the eye.

When assessing normal or borderline self-diagnosed dry eye subjects using aberrometry, combining lubricating eye drops and spray does not offer any benefit over individual products. However, subjects perceive a difference in comfort for all interventions after one hour.

Total higher order aberrations increase after laser assisted sub-epithelial keratectomy performed using a solid-state laser on myopes, but this causes no significant decrease in contrast sensitivity or increase in glare disability. Mean sensitivity and reliability indices for perimetry were comparable to pre-surgery results.

Multifocal contact lenses and intraocular lenses are designed to maximise vision when the patient is binocular, so any evaluation of the eyes individually is confounded by reduced individual visual acuity and visual quality. Different designs of aspheric multifocal contact lenses do not provide the same level of visual quality. Multifocal contact lenses adversely affect mean deviation values for perimetry and this should be considered when screening individuals with multifocal contact or intraocular lenses. Photographic image quality obtained through a multifocal contact or intraocular lens appears to be unchanged.

Future work should evaluate the effect of these anomalies in combination; with the aim of providing the best visual quality possible and supplying normative data for screening purposes.

Key words: dry eye, higher order aberrations, multifocal contact lens, refractive laser surgery, visual fields.

Dedicated to Elliot

ACKNOWLEDGEMENTS

I would like to thank my supervisors Dr Shehzad Naroo and Dr Frank Eperjesi for guidance, support and encouragement throughout this process. Additionally, I wish to thank Professor Sunil Shah and Rosemary Adkins who were instrumental to the completion of the thesis.

I owe a debt of gratitude to all the staff and students at Aston University who have helped me with advice or by participating in my experiments. I have also appreciated the friendship and support I have received while I have been at Aston, particularly from Clare Hayes, Lisa Baker and Stephanie Mroczkowska.

Finally I would like to thank friends and family for tolerating my focus on work and particularly my son Elliot for encouraging me to keep going and try my best.

CONTENTS

Chapter 4 - VISUAL EFFECTS AFTER REFRACTIVE SURGERY

Chapter 5 – PERIMETRY POST-REFRACTIVE SURGERY

Chapter 6 - PRECILENS C2MULTI VERSUS CIBA VISION AIR OPTIX™ AQUA MULTIFOCAL: A COMPARATIVE STUDY

LIST OF TABLES

LIST OF FIGURES

Chapter 1 INTRODUCTION

The median age of the UK population increased from 35.4 years to 39.7 years between 1985 and 2010 (United Kingdom National Statistics, 2013), resulting in an increased prevalence of presbyopia with just over a third of the population (22 million) aged over 50 years. Estimates show uncorrected presbyopia as one of the leading causes of disability in poorer countries (Holden et al., 2008), however, this condition impacts on quality of life, regardless of wealth, literacy or profession (Patel, 2007). The risk of other eye conditions including cataracts, macular degeneration and glaucoma increase with age (de Jong, 2013) and dry eye is accelerated by age (Tsubota et al., 2012). Refractive surgery is one of the most common elective ophthalmic surgery procedures performed worldwide (Solomon et al., 2009) and due to continual improvements in laser technology and ablation nomograms, has been recommended for surgeons performing 'delicate operations' (Lee et al., 2012). Many individuals have a desire to remain spectacle free following presbyopia, particularly following cataract surgery (Khor and Afshari, 2013) and there are several prescriptive and surgical approaches. Multifocal contact lenses and multifocal intraocular lenses counteract the effects of reduced amplitude of accommodation in the ageing eye by extending the ocular depth-of-focus (Plainis et al., 2013); although dry eye due to ageing, concurrent medication (Chia et al., 2003) or other aetiologies (including secondary to refractive surgery (Dooley et al., 2012) may confound contact lens wear. Within the growing presbyopic demographic there are therefore increased numbers of patients suffering from dry eye who have undergone refractive surgery; who wish to wear or are wearing a multifocal contact lens correction or who have been fitted with multifocal intraocular lenses. It is important for clinicians to understand the visual consequences and limitations to screening or monitoring for eye diseases in these individuals. The purpose of this body of work is to increase understanding and assess clinical implications of these anterior eye anomalies and their effects on visual quality.

The introductory chapter provides details of the anomalies investigated and a review of the current literature.

1.1 The tear film

The most anterior surface of the eye is the tear film. There have been many studies to measure the average thickness of the tear film and recent research has suggested a figure of approximately 3µm (Azartash et al., 2011). The anterior radius of the tear film has been approximated at 7.8mm with a refractive index of 1.336. This gives a surface power of 43.08 dioptres (Montés-Micó, 2007), which makes it the most powerful refracting surface as it represents the largest change in refractive index.

The tear film, however, is inherently variable in volume, composition and stability, particularly in patients with dry eye conditions. Despite its small volume, the tear film is complex and contains many elements to provide hydration to maintain corneal transparency, lubrication against the shear stresses of the lids and immunity against invading pathogens. The three main elements are: the outer lipid layer secreted by the meibomian glands, which acts to prevent evaporation by a system of polar and non-polar lipids (McCulley and Shine, 1997); the aqueous, a more fluid element secreted by the lacrimal glands; and a gradient of gel-like dissolved mucin element (Chen et al., 1998) secreted by goblet cells and the entire ocular surface epithelium (Watanabe et al., 1995). Maintenance of a smooth, intact tear film is essential for ocular comfort and the achievement of high quality retinal images. Every blink reconstitutes the tear film after which evaporation starts. The length of time it takes for the tear film to become disorganised and break down is called the tear film break up time. In normal eyes this usually occurs after approximately 10 seconds, however, in dry eye conditions the tear film can become unstable and break down within a few seconds (Lemp and Hamill Jr, 1973). Huang et al. showed that tear film changes in dry eye could lead to corneal surface irregularities which caused glare disability, however, in the early stages of dry

eye these changes were too subtle to be detected by corneal topography or contrast sensitivity (Huang et al., 2002). The two main mechanisms to affect visual quality are therefore tear instability and an irregular corneal surface. It is interesting to note that the tear film takes between 3 to 10 seconds to achieve its most regular state, therefore immediately after a blink the image quality may not be optimised (Nemeth et al., 2002).

1.2 Definition of dry eye

Dry eye has been defined by The Dry Eye Workshop (DEWS) as 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface' (Lemp, 2007). The 'Core Mechanism' of dry eye starts with increased evaporation leading to hyperosmolarity of the tear film. This initiates a cascade of inflammatory processes resulting in epithelial damage, mucin deficiency and reduced wettability of the cornea. Without intervention this becomes a vicious cycle (Lemp, 2007). Dry eye is typically described as either aqueous deficient or evaporative in origin, however, the aetiologies are not mutually exclusive and it has been reported that evaporation is the significant contributing factor in up to 78% of cases (Pult et al., 2012).

1.3 Risk factors for dry eye

Researchers have found that 52% of contact lens wearers, 23% of spectacle wearers and 7% of patients who have no optical prescription self-report dry eye in optometric practice (Nichols et al., 2005). Among the many proven risk factors for dry eye are: increased age, female gender, medication, connective tissue disease, radiation therapy and laser assisted in-situ keratamileusis (LASIK) or other refractive excimer laser surgery (Lemp, 2007). Symptoms of dry eye are often exacerbated by environmental conditions, e.g. low humidity (McCarty and McCarty, 2000) and tasks requiring

concentration, e.g. computer use (Nakaishi and Yamada, 1999, Himebaugh et al., 2009), although recreational activities are also implicated (Miljanovic et al., 2007). Increases in the number of people suffering from allergies has also contributed to the number of dry eye cases as allergic and inflammatory ocular surface conditions can have a destabilizing effect on the tear film (Fujishima et al., 1996). Smoking interferes with the lipid layer (Altinors et al., 2006) and meibomian gland dysfunction (MGD) is a major cause of evaporative dry eye, with the degradation of the lipid layer leading to rapid evaporation of the remaining tear film (Foulks and Borchman, 2010).

1.4 Clinical evaluation of dry eye

A wide variety of tests have been used to evaluate dry eye (McGinnigle et al., 2012), some more complex than others and with varying sensitivity and specificity. Lemp highlighted the problem of spectrum bias in many of the smaller studies investigating methods to investigate dry eye with regard to interpretation of sensitivity and specificity figures (Lemp, 2007). Recruitment of moderate to severe diseased states, more easily distinguished from normal, led to values and conclusions which could not be applied to a generalised dry eye population in a clinical setting containing many more mild cases.

1.4.1 Subjective evaluation of dry eye

Examination of a patient with dry eyes invariably starts with history and symptoms. In mild and moderate cases of dry eye, symptoms of discomfort and dryness are often the predominant features reported by between 30 and 80% of sufferers (Begley et al., 2003), although the lack of correlation between symptoms and signs are widely recognised (Begley et al., 2003, Hay et al., 1998, Johnson, 2009, Nichols et al., 2004a, Vitale et al., 2004). The variability of reported symptoms can be simplified by a defined list of questions to make comparisons between visits and also between patients more straightforward. Validated questionnaires are employed in research and clinical settings to screen individuals, thus ensuring consistency in recording symptomatic information

(Smith, 2007). They consist of a series of questions with values attributed to the answers, allowing the symptoms to be scored and the severity numerically recorded. The most widely used of these are the McMonnies Dry Eye Index and The Ocular Surface Disease Index (OSDI), the latter being deemed the most reliable (Schiffman et al., 2000, Nichols et al., 2004b). The limitation with both these questionnaires is the time required to complete them. Chalmers developed a five point questionnaire to distinguish between patients with and without dry eye (Chalmers et al., 2010). This questionnaire could be completed in less than a minute, making it more suitable for screening purposes.

1.4.2 Objective evaluation of dry eye

A scientific roundtable on dry eye ranked tear break up time (93%), corneal staining (85%), tear film assessment (76%), conjunctival staining (74%) and the Schirmer test (54%) as the most commonly used diagnostic tests for initial assessment of dry eye (Smith et al., 2008), although an earlier report had found symptom assessment (82.8%), fluorescein staining (55.5%) and tear break up time (40.7%) to be the most frequently used tests in cases with a dry eye diagnosis (Nichols et al., 2000). Standardized grading of corneal and conjunctival fluorescein staining have given this dye broad applicability as a dry-eye diagnostic test, particularly as an assessment tool in clinical studies of dry eye, however, the mechanism of staining is not fully understood (Morgan and Maldonado-Codina, 2009). Historically, the use of invasive techniques to evaluate the tear film may have compromised the results, which has led to the recommendation of ‘minimally invasive techniques’ for the diagnosis and monitoring of dry eye (Bron et al., 2007). Changes in the fluid volume and dynamics of the tear film can cause local variations in power of the tear film and this can produce higher-order wavefront aberrations. These imperfections can be measured and expressed as wave aberration errors, which describe how the phase of light is affected as it passes through the optical system of the eye. The use of wavefront sensing

aberrometers has been shown to be suitable for evaluating the optical qualities of the tear film (Li and Yoon, 2006) and assessing the effects of artificial tears (Montés-Micó et al., 2004a).

1.5 Treatment of dry eye

Three steps towards treating dry eye were identified in a European Ocular Surface Workshop held in Italy in 2009 (Rolando et al., 2010):

1. 'Patient education, monitoring the eyelid environment, use of artificial tear substitute and eyelid therapy'.

2. 'Addition of temporary anti-inflammatory agents, temporary punctual occlusion, secretagogue administration'.

3. 'Autologous serum and amniotic membrane.'

The most frequently used therapy for mild to moderate dry eye would be ocular lubricants in the form of drops (Doughty and Glavin, 2009). The exact mechanism of these products is difficult to identify as these preparations do not recreate the function of the tear film, but do seem to have a lubrication effect (Pflugfelder, 2007). Unpreserved drops are preferable; the most widely used preservative in artificial tears, benzalkonium chloride 0.01%, can destabilise the tear film and have cytotoxic effects, particularly when used more than four times a day (Tripathi and Tripathi, 1989). Short term exposure to benzalkonium chloride has been shown to: decrease goblet cell density (Herreras et al., 1992); cause tear film instability (Ishibashi et al., 2003); conjunctival squamous metaplasia and apoptosis (Pisella et al., 2004); disruption of the corneal epithelium barrier (Jong et al., 1994); and have possible proinflammatory effects (Pauly et al., 2007). Increased cost, difficulty instilling drops and compliance issues (including the fact that the patient has to carry sufficient vials when not at home)

(Berdy et al., 1992) has led to the development of different delivery systems to retard tear evaporation, such as liposomal sprays.

The lipid layer has a stabilising effect on the tear film, reducing evaporation by up to 95% (Lozato et al., 2001), although reduction of aqueous (the watery component of tears) has been shown to affect the stability of the lipid layer (Yokoi et al., 2008). Liposome sprays have been shown to increase lipid layer thickness and improve tear film stability in normal eyes for approximately 60 minutes following application to a closed eye (Craig et al., 2010). The delivery system offers an advantage in that it does not require preservatives and is easy to apply to closed lids, from where it migrates to augment the polar lipid layer which improves lipid spreading over the tear film. Recent research assessing comfort, non-invasive tear stability and tear meniscus height has shown that the only truly effective liposomal spray in the treatment of dry eye is Optrex Actimist (Optima Pharmazeutische GmbH) (Craig et al., 2010, Pult et al., 2012). Too little or inappropriate liposomal ingredients were thought to be the major factors contributing to the poor performance of newly developed competitors (Pult et al., 2012).

1.6 The tear film and optical quality

The tear film is the first refracting surface of the eye and local disruption or tear film breakup creates an irregular optical surface, which increases higher order aberrations and reduces image quality (Montés-Micó et al., 2005). The central corneal region has been shown to be susceptible to increased tear breakup in dry eyes when compared to normal controls (Liu et al., 2006). Koh et al. found significantly increased total higher order aberrations between 5 to 9 seconds after blinking compared with immediately after a blink (Koh et al., 2008a). Ferrer-Blasco et al. showed a correlation between Strehl ratio and tear breakup time in young normal subjects (Ferrer-Blasco et al., 2010). Xu et al. found an association between changes in tear menisci and tear breakup in normal subjects; however, there was a large variation in dynamic changes

in higher order aberrations, suggesting differences in tear quality and performance (Xu et al., 2011). A study by Thibos and co-workers demonstrated the significant effect of an unstable tear film and suggested that aberrometry using the Shack-Hartmann technique represented a good description of the optical imperfections of dry eye (Thibos and Hong, 1999). Montés-Micó and associates compared wavefront aberrations measured using the Zywave aberrometer (Bausch and Lomb, Irvine, CA, US) in dry and normal eyes. The dry eye group showed larger optical aberration values, in particular larger values in vertical coma compared to horizontal coma, whereas in normal eyes these values were more similar. This was attributed to asymmetric changes in the tear film thickness between the superior and inferior cornea, giving a sawtooth pattern and a marked upward curve of sequential higher order aberrations after each blink. There was also more positive spherical aberration, which they proposed was due to central thinning of the tear film in relation to the periphery (Montés-Micó et al., 2004b). There is concern that Shack-Hartmann aberrometry (Liu et al., 2010) lacks the necessary resolution to fully capture the optical disturbances associated with the rough corneal surface exposed by tear break-up (Koh et al., 2006a, Montés-Micó et al., 2004b).

Figure 1.1 Basic Design of a Shack-Hartmann aberrometer. Charman, W. N. (2005). Wavefront technology: past, present and future. Contact Lens and Anterior Eye, 28(2), 75-92.

Conventional analysis of Shack-Hartmann images quantifies aberrations based on displacement of a multitude of spots formed by an array of lenslets, each of which is the image of a retinal beacon of reflected light, however, macro- and micro-aberrations can excessively displace and blur the spots (Liu et al., 2010). These spots are ignored if conventional Zernike terms are used to describe the wavefront, with an effective smoothing of data, therefore an alternative algorithm may be required (Nam et al., 2011). Himebaugh et al. used local zonal analysis of measured wavefront slopes and suggested that very high order aberrations not included in conventional modal analysis contribute to reduced optical quality of the eye (Himebaugh et al., 2012).

Figure 1.2 Schematic raw SH data are shown in the top part of this figure. The left panel shows spot displacement (left arrow) as the basis of determination of macro-aberrations, while the right hand panel shows spot enlargement (right arrow) caused by micro-aberrations (Himebaugh et al., 2012)

1.7 The cornea

The average adult human cornea is between 11.5 to 12.0 mm in diameter (Rüfer et al., 2005) and approximately 0.5mm thick in the centre, increasing in thickness towards the periphery. Diseases associated with collagen disorders (including keratoconus) or endothelial-based corneal dystrophies (e.g., Fuchs endothelial dystrophy) have been shown to result in decreases or increases, respectively, of corneal central thicknesses beyond the normal variance (Doughty and Zaman, 2000). The prolate shape of the cornea (flatter in the periphery and steeper centrally) creates an aspheric optical system and relates to its biomechanical structure, in particular the rigid anterior stroma (anterior 120 µm). This is particularly important when considering the effects of refractive surgery, in either surface ablation procedures where it is removed, or LASIK where it is intersected (Müller et al., 2001). Until recently it was accepted that the human cornea consisted of 5 recognized layers; 3 cellular (epithelium, stroma, endothelium) and 2 interface (Bowman membrane, Decemet membrane). The recent discovery of 'Dua's Layer;' a 10.15 ± 3.6 µm acellular layer in between Decemet's membrane and the stroma (Dua et al., 2013) may have implications regarding the biomechanics of the cornea.

Figure 1.3 Light photomicrograph of resin section stained with toluidine blue showing a type-1 big bubble from which the Descemet's membrane has been peeled off centrally to reveal the Dua's layer (Dua HS, Faraj LH, Said DG, Gray T, and Lowe J. "Human Corneal Anatomy Redefined: A Novel Pre-Descemet's Layer (Dua's Layer)." *Ophthalmology* (2013).

The corneal epithelium is approximately 40-50 µm in central thickness. It is critical to the refractive power of the eye and is composed of nonkeratinized, stratified squamous epithelium 4 to 6 cell layers thick (Farjo et al., 2009). A population of limbal epithelial stem cells (LESCs) are responsible for maintaining the epithelium throughout life by providing a constant supply of new cells that replenish those constantly lost from the ocular surface during normal wear and tear and following injury (Daniels et al., 2001). The superficial epithelia are covered in microvilli and microplicae covered in a filamentous cell coat or glycocalyx which forms a scaffolding to bind mucins (Nichols et al., 1983) and allow hydrophilic spreading of the precorneal tear layer. The tear film also supplies immunological and growth factors that are critical for epithelial health,

proliferation and repair (Pflugfelder, 2011). The epithelial basement membrane comprises type IV collagen and laminin secreted by the basal cells. If damaged, fibronectin levels increase and healing can take up to 6 weeks during which time the bond between the epithelium and basement membrane is unstable and weak (Dua et al., 1994). Bowman's layer is approximately 15 μm thick and is positioned between the epithelial basement membrane and the anterior stroma populated with keratocytes. There is evidence that chemotactic influences mediated by cytokines from the epithelium have a critical role in formation and maintenance of the acellularity of this layer (Wilson and Hong, 2000). The corneal stroma comprises 80% to 85% of the overall thickness of the cornea. The size and organization of dense, regularly packed collagen fibrils arranged as orthogonal layers or lamellae influence the biomechanical and optical properties. The closer packing of stromal collagen fibrils over the centre of the cornea is thought to predict a higher central refractive index (Boote et al., 2003). Keratocytes are the major cell type in the stroma and maintain the extracellular matrix (ECM) by synthesizing collagen molecules and glycosaminoglycans in addition to creating matrix metalloproteases (MMPs). The majority of the keratocytes are in the anterior stroma are comprised of 25-30% corneal crystallins; a soluble protein thought to be responsible for minimizing light scattering and maintaining corneal transparency (Jester et al., 1999). The stroma is maintained in a relatively deturgesced state (78% water content) by the activity of the endothelial cells (Geroski et al., 1985). Endothelial cell density and topography change throughout life, declining from 3000 to 4000 cells/ mm^2 to around 2600 cells/ mm^2 from the second to eighth decade of life with a reduction from 75 to 60% hexagonal cells (Yee et al., 1985). Endothelial cell density is approximately 10% higher in the peripheral cornea, with a greater discrepancy in older patients (Amann et al., 2003). Researchers have demonstrated that peripheral endothelial cells can spread and cover damaged areas by remodelling (Edelhauser, 2000), however, the presence of stem-cell markers has led to the belief that the endothelium may be capable of regeneration (Woodward and Edelhauser, 2011).

The cornea is avascular; however, components of the blood are supplied by end branches of the facial and ophthalmic arteries via the aqueous humour and tear film. The corneal nerve sensations are derived from the nasociliary branch of the first (ophthalmic) division of the trigeminal nerve, although the inferior cornea can receive some of its innervation from the maxillary branch (Ruskell, 1974). Nerves enter the stroma radially in thick trunks forming plexiform arrangements, which eventually perforate Bowman's membrane to provide a rich plexus beneath the basal epithelial layer (Müller et al., 1996). Sympathetic innervation is supplied by the superior cervical ganglion; however, the nerve fibres are scarce in human corneas (Toivanen et al., 1987).

1.7.1 Surgery and the cornea

Intraocular and corneal refractive surgery can result in injury to the cornea. One of the most serious complications of anterior segment surgery is injury or detachment of Decemet's membrane, which can potentially lead to significant endothelial cell loss and decompensation (Al-Mezaine, 2010). The risk factors include improper surgical technique, suboptimal quality of equipment (Yi and Dana, 2002) and phacoemulsification of hard nuclear cataracts (Bourne et al., 2004). Deposition of a new basement membrane requires endothelial cell migration, which led to the development of an air bubble tamponade to hold the loose membrane tags against the posterior cornea to facilitate healing (Ti et al., 2013). Corneal oedema can occur as a direct result of phacoemulsification specifically as a result of direct mechanical trauma, ultrasound energy or the biomechanical and mechanical effects of the irrigating solution (Polack and Sugar, 1977). The pH, osmolarity, temperature and method of preservation of irrigation solutions and intraocular medication are also critical in maintaining endothelial cell health (Edelhauser et al., 1976, Anderson and Edelhauser, 1999).

The biological diversity in the corneal wound healing response is a major factor in the outcome of refractive surgery procedures and determines overcorrection, undercorrection, regression, haze and refractive instability (Netto et al., 2005). Laser ablation injuries to the cornea can stimulate a fibrotic repair response leading to opacity and contraction, which may also alter the corneal curvature. Control of fibroblast activation can promote regeneration as epithelial-stromal interaction mediates fibrotic repair in the cornea, where healing occurs avascularly (Stramer et al., 2003, Fini, 1999). The healing responses are different in surface and deep stromal ablation procedures; the fibrotic response is usually stronger after surface procedures, possibly as a consequence of the disruption to the basement membrane (Stramer et al., 2003, Nakamura et al., 2001). Epithelial damage without basement membrane loss results in cellular replacement without fibrosis (Zieske et al., 2001). It has been reported that preservation of the integrity of the central corneal epithelium results in less epithelial-stromal cell interaction and subsequent lower rates of keratocyte aptosis and necrosis following LASIK (Mohan et al., 2003). Less keratocyte proliferation and myofibroblast differentiation appears to correlate with less regression and haze (O'Brien et al., 1998). Regression after LASIK is attributable to epithelial hyperplasia (increase of the epithelial thickness) and stromal remodelling (Lohmann and Guell, 1998, Reinstein et al., 1999). Haze can be present at the flap margins where there is direct contact between the normal and activated keratocytes in the stromal tissue (Vesaluoma et al., 2000); or centrally due to diffuse lamellar keratitis (inflammatory cells at the flap interface) (Smith and Maloney, 1998), donut shaped flaps or the retention of epithelial debris in the interface (Wilson, 1998). Laser subepithelial keratectomy (LASEK) is a modified photorefractive keratectomy (PRK) technique where ethanol is used to create an epithelial flap which is repositioned after surgery. It has been reported that this reduces pain, promotes faster visual recovery and less haze (Vinciguerra et al., 2003) by serving as a mechanical barrier to protect the stroma from growth factors in the tear film (Lee et al., 2002). This advantage has been contested (Litwak et al., 2002) and the

viability of the removed epithelial cell layer has been questioned, particularly re-adhesion when the basement membrane is no longer present on the stroma (Espana et al., 2003).

1.8 The crystalline lens and accommodative anatomy

The ciliary muscle is composed of muscle fibres of longitudinal, radial and circular orientations acting as a single functional entity with the muscle fibres contracting as a unit (Charman 2008). The ciliary muscle is surrounded on the inner surface by the highly vascularised ciliary body, which provides oxygen and nutrients to the ciliary muscle. The ciliary body is subdivided anatomically into the anterior pars plicata (the ciliary processes) and the posterior pars plana region, which extends to the ora serrata. There are two groups of fine, elastic zonular fibres. The anterior zonular fibres insert into the lens capsule all around the lens equator and they extend across the circumlental space to attach along the walls of the ciliary processes of the anterior ciliary body (Glasser and Campbell 1999). The posterior zonular fibres, also known as vitreous zonules (Lutjen-Drecoll et al. 2010), extend from the walls of the ciliary processes of the ciliary body, posteriorly towards the posterior insertion of the ciliary muscle near the ora serrata. The lens can be broadly differentiated into the inner nucleus and the surrounding cortex. The lens is composed of 65% water and 35% crystallins protein, which is highly concentrated and has a uniform structure to facilitate transparency (Andley, 2007). It can be divided in to three distinct components; the epithelium located beneath the anterior capsule, the densely packed lens fibres which constitute the bulk of the lens and the elastic capsule composed of pliable collagen fibres which allow the lens to change shape (Stafford 2001). The posterior lens surface has a steeper radius of curvature in comparison to the anterior lens surface (Koretz et al., 2004) and the refractive index of the lens increases towards the centre of the lens as lens fibres are created throughout life but not discarded (Al-Ghoul and Costello, 1997).

1.9 Presbyopia

Presbyopia is a gradual reduction of accommodative ability due to the loss of flexibility of the crystalline lens and creates refractive error affecting the near vision. The combination of the high prevalence in older adults and the low rates of spectacle access in some global communities mean that presbyopia is a significant burden across the world (Holden et al. 2008). The lenticular model is supported by research showing established presbyopes are still able to contract the ciliary muscle during accommodation, despite age-related morphological changes to the muscle (Sheppard and Davies, 2011). A meta-analysis of sex differences in presbyopia found significant differences in the power for near vision addition requirements between men and women, citing preferred viewing distances due to arm length or specific tasks, occupation, indoor light levels or uncorrected hyperopia as factors contributing to higher prescriptions for women (Hickenbotham et al., 2012). In the past, the usual remedy for presbyopia was to wear reading glasses, multifocal lenses (bifocal or progressive) or use magnifying devices, however, monovision and multifocal contact lenses and surgical remedies for presbyopia are also available (see section 6.2). A variety of different kinds of surgical procedures have been considered for correction of the presbyopic eye, although at present vision cannot be restored to the pre-presbyopic state. Surgical expansion of the sclera, where radial slits in the sclera (radial sclerotomy) or polymethyl methacrylate (PMMA) scleral expansion bands are inserted into four scleral tunnel incisions overlying the ciliary muscle to expand the diameter of the sclera over the ciliary muscle (Qazi 2002) has not been shown to restore accommodation. Femtosecond lasers have been utilised for multifocal refractive surgical procedures to modify the curvature of the cornea, but this technique increases the depth of field of the eye rather than changing the accommodative response and therefore it is unlikely that surgical manipulation could induce significant changes to restore accommodation. Corneal inlays have the advantage of being minimally invasive

and easily reversible for the treatment of presbyopia, however, this is a relatively new development and the long-term effects have not been evaluated (Limnopoulou et al 2013). Multifocal and accommodating intraocular lenses (in addition to monovision strategies) are becoming more popular and will be discussed in detail in section 1.11.

1.10 Cataracts

Cataract is the major cause of blindness around the world (51%) and the most prevalent ocular disease (World Health Organization 2010). Cataract describes any opacity of the lens from a small local opacity to diffuse loss of transparency, however to be clinically significant there must be a measurable reduction in visual acuity or functional impairment. Ageing is the principal cause of cataracts (Mitchell et al., 1997, Livingston et al., 1994), but this is further complicated by cumulative factors e.g. causes linked to systemic and ocular diseases in addition to mechanical, chemical (including prescribed drug induced changes) radiation trauma and unknown risk factors (Robman and Taylor, 2005). Diabetics with cataract have a higher morbidity than those without (Cohen et al., 1990). Developmental abnormalities can also cause cataracts (Lloyd et al., 1992).

A systematic review of large sample prevalence studies specifying cataract accompanied by reduced acuity in subjects over 40 years old, found a prevalence of 15-30%, increasing to 40% in the over 70 age group and 60% in the over 75 age group. Women were more commonly affected than men, particularly in the higher age groups (Rsdeep and De Catarata, 2006).

Age related cataracts are generally categorised into cortical, nuclear or posterior subcapsular cataracts although they are not mutually exclusive. There are several other photograph based classifications systems in use to assist the grading of cataract extent and location including the World Health Organisation simplified cataract system (Thylefors et al., 2002), the Oxford Clinical Cataract Classification and Grading System

(Sparrow et al., 1986) and the Lens Opacity Classification System (LOCS, LOCS II, LOCS III) (Chylack Jr et al., 1988, Chylack Jr et al., 1989, Chylack et al., 1993). The LOCS system uses photographs of slit lamp cross sections of the lens as references for grading nuclear opalescence and nuclear colour and photographs of the lens seen by retroillumination for grading cortical and posterior subcapsular cataract. In most clinical settings the reference photographs are not available so a less sensitive four point grading system modified from LOCS II (Chylack Jr et al., 1989) is used. This is the most commonly used system in the UK (Professor Sunil Shah, personal communication).

1.10.1 Cataract surgery

Under most circumstances, cataracts are removed by extracapsular cataract extraction (ECCE) using either phacoemulsification or nuclear expression and the lens capsule is retained so that it can hold an intraocular lens. Although intracapsular cataract extraction (ICCE), where the lens and capsule are removed, is still used under certain special circumstances where an intraocular lens (IOL) cannot be introduced or in some parts of the world where access to IOLs may be limited (Jaffe et al., 1990).

During extracapsular cataract extraction by phacoemulsification, the central part of the anterior capsule is cut and removed and then an ultrasonic probe is used to emulsify the nucleus and extract it using a suction device. The posterior lens capsule is left in place allowing placement of a posterior chamber IOL in to the capsular bag (Peckar, 1991). This technique can be performed through incisions less than 2mm allowing rapid healing and improved visual outcomes (Hoffman et al., 2005). This has led to the transition of cataract surgery from inpatient to outpatient surgery, reducing the costs whilst maintaining positive surgical outcomes (Gogate et al., 2003).

1.11 Modern multifocal intraocular lens designs

Cataract surgery techniques and IOLs have evolved considerably over the last few decades. Monofocal intraocular lenses are designed to provide good visual acuity at a single fixed focal length, usually in the distance, so an additional near and intermediate spectacle correction is required for near tasks. Spherical IOLs induce spherical aberration compounding the effect of the positive spherical aberration induced by the cornea. Aspheric IOLs were developed to counter this, improving contrast sensitivity and visual acuity; however, the benefits are reduced with a smaller pupil size over spherical IOLs (Kohnen et al., 2009).

The importance of independence from glasses was highlighted in a study by Luo et al. who found that 10% of patients with presbyopia would be willing to trade 5% of their life expectancy to be free from presbyopia (Luo et al., 2008). Replicating the optics of the youthful lens is not currently possible; however, development of multifocal IOLS is one response to this challenge.

Multifocal IOLs (MIOL) provide high levels of spectacle independence with a mechanism of action independent of ciliary body function. Although monofocal IOLs can provide near correction utilizing monovision or ‘blended vision’ techniques, there are sacrifices in binocularity and effectivity is limited to a difference of 1.50D. Different designs of MIOL have different optical properties affecting image quality; refractive designs can be concentric or sectorial, while diffractive designs are either partially or fully diffractive.

1.11.1 Zonal multifocal designs

Multi-zone concentric refractive MIOLs have several concentric zones that differ in curvature creating two or more refractive powers. The first multifocal IOL approved for use in the US was AMO array (Abbot Medical Optics Inc., Santa Ana, CA, USA) in 1997. This lens had a spherical posterior surface optic and centre-distance zone

surrounded by four alternating near and far zones (Steinert et al., 1999). Steinert et al. conducted a prospective, non-randomized, fellow eye comparative trial measuring mean uncorrected and corrected distance and near visual acuity for the year after surgery. No difference was found for distance visual acuity and near acuity was almost two lines better, however, subjects reported dysphotopsia (glare and halos) and reduced low-contrast visual acuity (Steinert et al., 1999).

Later designs based on this principal are the Rezoom (Abbot Medical Optics Inc., Santa Ana, CA, USA) which incorporates an aberration reducing aspheric posterior surface and the more recent MFlex (Rayner Intraocular lenses Ltd, Hove, UK), which has a choice of two additions and either four or five refractive zones depending on the power of the IOL. Having multiple zones reduces dependence on pupil size and mimimises the effects of decentration, however, smaller pupil diameters direct the majority of the light to the distance focal point. At a pupil size of 5mm, two thirds of the light is dedicated to the distance (Lane et al., 2006).

1.11.2 Sectorial refractive multifocal intraocular lenses

Sectorial refractive MIOLs are rotationally asymmetrical; the reading addition is in a specific section of the lens. Although the lenses have a similar appearance to bifocal spectacle lenses, the mechanism of action is still simultaneous in common with all MIOL rather than translating. This type of lens has not been extensively tested, however, the Lentis MPlus (Oculentis GmbH, Berlin, Germany), was recently found to induce positive primary coma which caused a reduction in near vision from the induced optical blur (Ramón et al., 2012).

1.11.3 Diffractive multifocal intraocular lenses

Diffractive MIOLs use the principal of diffraction to create two or more focal points; the boundary of each ring creates an interference pattern of light and the separation between the ring edges determines the power of the effective addition. The limitation of

these lenses is the light lost to higher orders, creating aberrations. In a +4.00D diffractive MFIOL this has been calculated to be 18% (Hütz et al., 2006).

Fully diffractive MIOLs are pupil-independent maintaining the split of light between distance and near e.g. Tecnis ZM900 (Abbott Medical Optics Inc., Santa Ana, CA, USA). This offers a high level of near acuity and spectacle independence when compared with monofocal and refractive concentric designs of IOLs. There were also fewer photic complaints and improved patient satisfaction when compared with Rezoom (Abbot Medical Optics Inc., Santa Ana, CA, USA) (Cillino et al., 2008).

Partially diffractive MIOLs have the diffractive pattern over a specific area of the optic e.g. ReSTOR (Alcon, Fort Worth, Texas, US), which has a single refractive surface dedicated to distance surrounding the diffractive area. The grating on the anterior surface of the lens is apodized which means the step height of each concentric ring is lower than that of the previous more central step. The posterior of the lens is convex aspheric to offset positive corneal spherical aberration. The lens is pupil size dependent, the larger the pupil, the greater the distribution of light to the distance. Less than 10% of patients reported severe halos or glare with the +4.0 MIOL (Vingolo et al., 2007), however complaints did arise regarding the intermediate vision (Vingolo et al., 2007, Cionni et al., 2009, de Vries et al., 2010). This prompted the development of a +3.0 version resulting in improvements to intermediate visual acuity, a more realistic working distance, less detrimental effects on distance visual acuity and reduced higher-order aberrations (de Vries et al., 2010). A recent study found that in bright lighting conditions, MIOLs with a diffractive component provided the best reading performance when compared with monofocal and refractive MIOLs (Rasp et al., 2012).

1.11.4 Management of patients who have multifocal intraocular lenses

Many recent studies have evaluated patient dissatisfaction after implantation of multifocal intraocular lenses. The established compromises of visual function beyond

reduced distance or near vision include reduced contrast sensitivity, poor intermediate visual acuity, positive or negative dysphotopsia. De Vries et al. conducted a retrospective review of seventy six eyes of forty nine patients and summarised the perceived aetiology of complaints. Ametropia, posterior capsular thickening and IOL design factors were the chief complaints, however, there were five cases affected by corneal dystrophies. Corneal dystrophy can cause a decrease in visual acuity (Pogorelov et al., 2006) and contrast sensitivity and an increase in glare (Weiss, 2007). This highlights a key problem with multifocal IOL implantation. Not only is it difficult to assess and monitor pre-existing conditions, it may also be difficult to screen for new conditions, particularly when the symptoms overlap with known effects caused by MIOLs. Age is a risk factor for many diseases affecting the eye including glaucoma (Topouzis et al., 2011), macular degeneration (Minassian et al., 2011), diabetes (Holman et al., 2011) and vascular diseases (Roger et al., 2011). There is also the recent sharp increase in the prevalence of obesity, which is known to increase the risk of many vascular diseases, although the risk of obesity alone on the eye is as yet unknown (Cheung and Wong, 2007).

Despite Hawkins (2003) establishing the correlation between decreased contrast sensitivity and visual field loss in patients with glaucoma, contrast sensitivity testing is not routinely conducted during an eye examination. Therefore, clinicians are relying on the visual field plot to assess results. A study investigating the effect of a diffractive MIOL with the Humphrey Field Analyzer using a 30-2 grid and the Swedish Interactive Threshold Algorithm (SITA) standard strategy found a reduction in visual sensitivity (Aychoua et al., 2013). There have been reports of difficulty focussing on crystals appearing and disappearing during vitreous surgery due to focussing difficulties through a MIOL (Kawamura et al., 2008); and focussing issues, decreased contrast sensitivity and ghost images during another surgical case where the patient had a MIOL (Yoshino et al., 2010). A study comparing 38 eyes of 19 patients with a diffractive

multifocal IOL against 29 eyes of 18 patients with a monofocal IOL found wavy lines on optical coherence tomography line-scanning image (Inoue et al., 2009). Inoue went on to evaluate images of a grating target placed in a model eye viewed through MIOLs. It was concluded that refractive and diffractive multifocal IOLs blur the grating target, but less so with the wide-angle viewing system. The peripheral multifocal optical zone was thought to be more influential on the quality of the images because the blurring was most pronounced in the periphery (Inoue et al., 2011).

1.12 Summary

This body of work will: evaluate a new multifocal contact lens; validate new equipment to investigate visual quality; assess visual quality following application of ocular lubricants in normal and dry eyes; assess visual effects of refractive laser surgery and investigate the effect of multifocal lens designs on visual fields and photographic image quality. Evaluating the new design of multifocal contact lens will help to give insight in to what visual compromises are acceptable to patients and how to better meet their expectations. The auto-refractor function of the new Nidek OPD-Scan III aberrometer (Nidek Technologies, Gamagori, Japan) will be assessed in comparison to existing technology. Lubricants have previously been assessed by aberrometry, however, not in combination. It is interesting to find novel ways of using existing products to assess if a combination is more beneficial to the patient than the individual products. Higher order aberrations, glare sensitivity and visual fields following LASEK using a solid state laser platform has not previously been assessed and therefore this chapter will provide comparisons to other laser platforms and techniques. Multifocal contact lenses are a compromise and it is interesting to look at this from the patient's and clinician's perspective with representations of the visual field and a comparative image obtained through single- and multi-focal optics.

Chapter 2 – OBJECTIVE MEASUREMENT OF OCULAR ABERRATIONS

2.1 Introduction

The experimental chapters in this thesis investigate visual quality using a range of instruments and techniques to address the gaps in current knowledge. Visual acuity is the most frequently used indicator of spatial vision in clinical studies, although it does not correlate well with other spatial vision measures such as contrast sensitivity, low-contrast acuity or visual acuity in the presence of glare (Haegerstrom-Portnoy et al., 2000). A low correlation between acuity and contrast sensitivity may suggest that different spatial channels are detecting the targets (Elliott et al., 1990). Applegate investigated the effect of different coefficients of Zernike polynomials on visual acuity and found that individuals could correctly identify highly aberrated letters. He concluded that visual acuity is a good clinical tool, however, it was not suitable to detect subtle improvements in higher order aberrations (Applegate 2003a).

2.2 Objective measurement of refractive error

Historically, the only objective clinical measurement of refractive errors was determined by retinoscopy; a technique requiring additional lenses in front of the eye to quantify the result. This technique is completely reliant on the subjective responses and skill of the examiner. Autorefractors have been available in some form since the late 1960s and are easier to operate and far quicker than retinoscopy (Wood, 1987). The application of adaptive optics, wavefront science and aberrometry (Liang et al., 1994) to vision care has led to the development of instruments that can measure and correct human vision at the lower, second radial order (sphere [defocus] and cylinder) and also higher order aberrations.

A large number of different techniques have been developed for measuring the eye's aberrations including the crossed-cylinder aberroscope (Walsh, 1984), the spatially resolved refractometer (He et al., 1998), the laser ray-tracing method (Navarro, 1999),

phase-retrieval from double pass images (Iglesias, 1998), the pyramidal sensor (Iglesias, 2002) and the Hartmann-Shack (HS) sensor (Liang et al., 1994).

2.2.1 Autorefractors

Autorefraction is widely used in clinical ophthalmic practice, most commonly as a starting point for refraction, which is then modified subjectively. These instruments have also been used within research to evaluate the refractive state (Salmon et al., 2003, Cheng et al., 2003, Suryakumar and Bobier, 2003, O'Connor et al., 2006) and the accommodative response of the human eye (Wolffsohn et al., 2001, Win-Hall et al., 2010, Hazel et al., 2003). The accuracy and repeatability of the measurement of higher order aberrations is vital, although several readings are required in the planning of a custom surgical refractive correction, as variations in measurement can be caused by a combination of misalignment errors and small drifts in the measuring equipment (Davies et al., 2003b). These variations, however, are generally within the clinicians' normal operation range for lower order aberrations when the average reading is used, and on this basis a study has suggested that non-cycloplegic autorefraction could be used for general studies of children's development (Cheng et al., 2003), as it has been shown to identify hypermetropic children with reasonable accuracy without the use of cycloplegic refraction (Williams et al., 2008). Suryakumar et al. specified that when assessing non-cycloplegic refractive states in pre-school children, the design of the autorefractor was crucial to stabilize and relax accommodation. Instruments with close working distances underestimated hypermetropia, however, those with large working distances and distant fixation targets were more accurate (Suryakumar and Bobier, 2003). Choi et al. validated a portable photorefractor (infrared photoretinoscope) which measured both eyes simultaneously, giving interpupillary distance, pupil size and information on the alignment of the eyes at the same time. They claimed the 'interesting' target at 3m prevented the camera at 1m acting as a significant stimulus to accommodation, however, the dynamic range was smaller than a conventional

autorefractor by a factor of approximately two (Choi et al., 2000). The reliability of autorefraction decreases in some circumstances, such as in eyes with media opacities and IOLs, due to the scattering of the infrared beam used by these instruments (Villada et al., 1992, Raj et al., 1991). Studies evaluating autorefraction after implantation of intraocular lenses have shown conflicting results depending on whether the lens was refractive or diffractive when using autorefractors based on Scheiner's double pinhole principle, where autorefraction is measured with infrared light reflected through small apertures. In the case of the refractive intraocular lens (ReZoom IOL), where the multifocality changes the refraction based on pupil size, the spherical values were underestimated by approximately 1.00D, although the cylindrical components were reasonably accurate. This was attributed to the optical path of infrared light passing through different zones during fluctuations of eye movements (Muñoz et al., 2007). For a diffractive intraocular lens which uses a diffractive grating and is independent of pupil size, the spherical value was more accurate than the cylinder. The authors considered this to be within acceptable limits for clinical use, however, they cited irregular astigmatism and displacement or tilting of the IOL as possible causes of inaccuracy (Bissen-Miyajima et al., 2010). A study investigating the factors influencing the reliability (accuracy) of autorefractometry before and after laser in situ keratomileusis (LASIK) for myopia and myopic astigmatism found autorefraction to be less accurate following LASIK. The reliability of the autorefractor was influenced by the optic zone and the preoperative amount of myopia; higher myopia and smaller optic zones determined more myopic results (Mirshahi et al., 2010).

Autorefraction in adults has previously shown good reliability and high accuracy when compared to subjective refraction (Mallen et al., 2001, Davies et al., 2003a, Cleary et al., 2009, Sheppard and Davies, 2010, Shneor et al., 2011). The Nidek OPD-Scan III is a new instrument and this chapter will detail the clinical evaluation performed to assess

its validity and reliability as an autorefractor compared with non-cycloplegic subjective refraction.

2.3 Evaluation of the auto-refraction function of the Nidek OPD-Scan III

The Nidek OPD-Scan III is an aberrometer/corneal topographer workstation. The instrument is operated via a touch screen and also provides autorefractometry, keratometry and pupillometry functions. The unit plots sixteen different maps to provide information on the corneal shape, wavefront, internal aberrations and visual quality of the eye and has particular application in the assessment and management of keratoconus, pre and post-operative cataracts and for refractive laser surgery. It has a measurement range of -20.00 to +22.00D, 0 to ± 22.00D cylinder and 0 to 180° axis, with a minimum measurable pupil diameter of 2.6mm. All measurements are performed in one sitting without moving the patient, so the data from all modalities are aligned and registered with respect to each other. The instrument uses the principle of skiascopic phase difference to measure the time delay between central and peripheral fundus reflexes (MacRae and Fujieda, 2000). This technique can measure normal through to highly aberrated eyes as there is no crossover of data points. A scanning infrared slit beam is projected through a chopper wheel rotating at high speed and the reflected light is captured by an array of rotating photo-detectors covering 360° within the eye in 1° increments. This provides 2520 wavefront data points within a pupil diameter of up to 9.5mm. A built-in eye tracker accounts for eye movements that may occur during measurements. The raw data is plotted in refractive power maps which are converted to conventional wavefront maps and graphs. The difference in power across the pupil is used to generate the wavefront and autorefraction data (Buscemi, 2004).

Figure 2.1 The Nidek OPD Scan III courtesy of Nidek Technologies, Gamagori, Japan.

2.3.1 Study aim

The purpose of this study was to assess validity and repeatability of the Nidek OPD-Scan III for measurement of refractive error in non-cyclopleged eyes compared with subjective refraction as performed by an experienced eye care practitioner. The validity describes accuracy of the instrument; in this case how close the measurement is to subjective refraction. The repeatability is the extent to which the results obtained by the aberrometer are reproducible within the same session and between different sessions.

2.3.2 Sample size

An estimate of mean difference between objective and subjective methods of determining spectacle prescription was determined from previous studies to calculate the effect size (Eng. 2003). The maximum Sample size was calculated using G*Power

3.1 (Faul et al., 2007) using a two way paired t-test to show a medium effect size with 95% power and an alpha level of 0.05. The maximum number of subjects required was 54 and therefore 59 subjects were recruited to ensure adequate statistical power and allow for drop-out.

2.3.3 Subjects

The study was approved by the institutional ethics committee and the research followed the tenets of the Declaration of Helsinki. The nature of the study was explained to the participants and written, informed consent was obtained. Exclusion criteria were amblyopia, due to the associated difficulties obtaining reliable refraction results; contact lens wear within the previous week to avoid unreliable results due to corneal irregularity and subjects who had not been seen within the previous six months for routine eye examinations (including refraction) at the institution eye clinics, to ensure the exclusion criteria of ocular pathologies could be verified.

2.3.4 Experimental procedure

Subjective refraction was conducted using a chart at 6m on both eyes of each subject by the same investigator (SM) before autorefraction to maintain masking; however, the patient's previous clinical records were available at the time of testing and were used as a starting point for subjective refraction in most cases. Subjective refraction was performed using a trial frame and BVD of 12mm. Monocular best sphere and Jackson cross-cylinder technique were followed by binocular balancing (Humphris technique) to determine the subjective refraction. The endpoint criterion was maximum plus sphere and minimum minus cylinder power maintaining the best visual acuity, which was recorded in logMAR. The refraction was recorded to the nearest 0.25DS, 0.25DC and 2.5°.

Autorefraction was performed by the same investigator (SM) according to the manufacturer's instructions using the autotracking and autoshot functions. The subject

was instructed to fixate on the image of a hot-air balloon (the device has an autofogging mechanism to relax the accommodation) and the measurements were taken and readings printed. The machine automatically tests each eye three times and the representative value indicated by parentheses was used for comparison with subjective refraction; the accuracy was set to the nearest 0.25DS, 0.25DC and 1°. The auto-refraction result was inserted in a trial frame at BVD 12mm and visual acuity measured in the same way as for subjective refraction. The measurements were repeated on 14 subjects (28 eyes) at a different session within the same week to assess inter-session repeatability. Three automatic consecutive measurements were taken and the average was compared with the initial measurement averages taken for sphere and cylinder power. Intra-session repeatability was calculated by comparing the standard deviation of the three repeated readings on 14 subjects (28 eyes) within the same session.

2.3.5 Statistical analysis

Subjective and objective refraction results were entered into a Microsoft Excel spreadsheet. The mean spherical equivalent (MSE) was calculated for each refraction, by adding half of the cylinder power to the sphere. The difficulties in analysing cylinders in standard notation have been established (Bullimore et al., 1998), so power vectors (Thibos et al., 1997) were computed at axis 0 and 45, represented by the equations J_o and $J_{45,}$ respectively.

J_o = - (cylinder/2) cos (2 x axis)

J_{45} = - (cylinder/2) sin (2 x axis)

Agreement between the subjective and autorefraction methods was evaluated by calculating the bias (mean of differences) between the techniques and the 95% limits of agreement (LoA = mean difference ± 1.96 x standard deviation of the difference) as described by Bland and Altman (Bland and Altman, 1986). Normally distributed

continuous data underwent parametric statistical analysis. Normality was confirmed for the data sets using Kolmogarov-Smirnov, $p > 0.05$. Differences between the methods were compared using two-tailed paired t-tests ($p = 0.05$). Both eyes were included in the analysis to make a fair comparison with the most recent study by Schneor (2011). The implications for including measurements taken from the right and left eye of a subject are detailed in the discussion (Armstrong 2013).

2.4 Results

A total of 54 participants (108 eyes, 29 women, 25 men) with a mean age of 23.7 (SD 9.5) years (range 5 to 69, median 20 years) were included. The refractive error of the sample represented by the subjective refraction ranged from -10.75 to + 4.00DS, the mean spherical equivalent (MSE) mean was -3.06DS ± 2.7. The maximum amount of measured astigmatism was 4.50DC.

The graphs show the upper and lower 95% confidence intervals, which indicate the maximum and minimum error in reading for the autorefractor in 95% of cases, compared with the subjective refraction values.

For the spherical component, the mean difference between the Nidek OPD-Scan III and subjective refraction was -0.19 ± 0.36DS; $p = <0.01$, the 95% LoA between the methods were -0.50 to 0.88DS. For the mean spherical equivalent (MSE) the difference was -0.19 ± 0.35DS; $p = <0.01$, the 95% LoA between the methods were -0.51 to 0.89DS. There was little bias with respect to the sign or magnitude of the refractive error (Figure 2.2). Approximately 74% of the Nidek OPD-Scan III results were within ± 0.25DS and 90% within ± 0.50DS of the spherical components of the prescription (Figure 2.2).

Figure 2.2 Difference in spherical component and Mean Spherical Equivalent (MSE) between Nidek OPD-Scan III autorefractor and subjective refraction. The mean bias for spherical component is indicated by the solid line and the 95% confidence limits are indicated by the dotted lines (n = 108 eyes of 54 subjects).

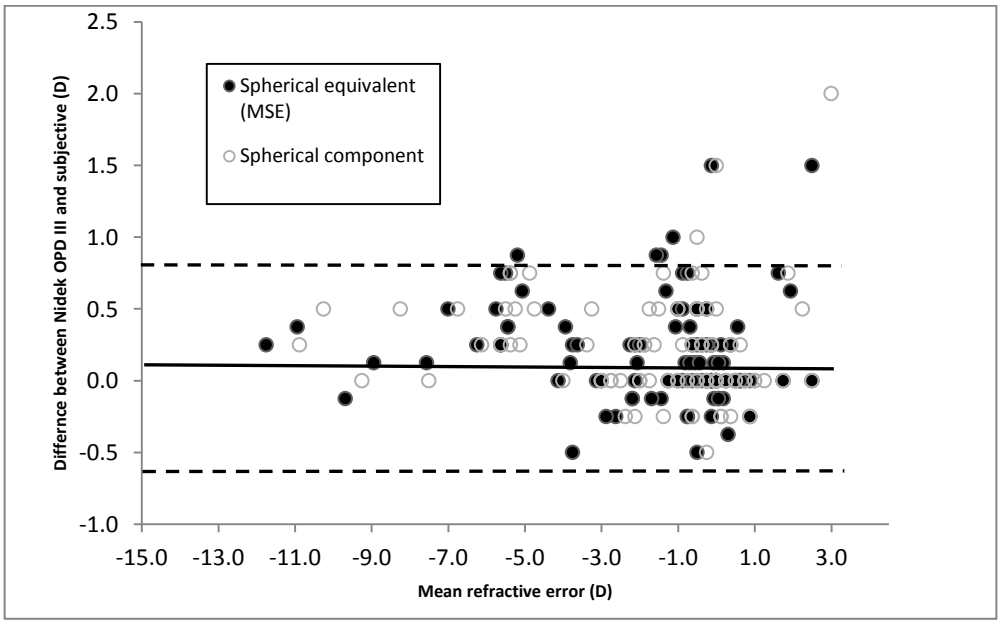
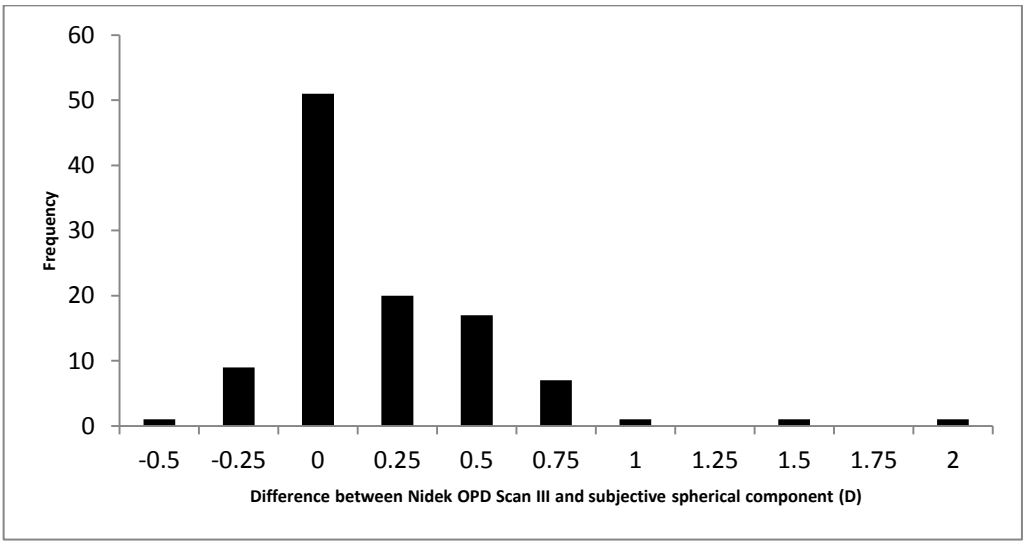


Figure 2.3 Comparison of the frequency of differences between Nidek OPD-Scan III autorefractor and subjective refraction for the spherical component (n = 108 eyes of 54 subjects).



There appears to be a slightly negative bias in the accuracy of the Nidek OPD-Scan III, with the most extreme outlying value being that of a 20 year old hyperope.

For the cylindrical component, the mean difference between the Nidek OPD-Scan III and subjective refraction was -0.002 ± 0.23D; p = 0.9, the 95% LoA between the methods were -0.46 to 0.46D. There was no significant bias.

For the cylindrical vectors, the mean difference between the Nidek OPD-Scan III and subjective refraction for the horizontal component was -0.06 ± 0.38DC p = 0.3, the 95% LoA between the methods were -0.81 to 0.68DC. The graph indicates that the autorefractor readings were very slightly biased towards the negative cylinder power (Figure 2.4).

Figure 2.4 Difference in J_O cylindrical component between Nidek OPD-Scan III autorefractor and subjective refraction. The mean bias is indicated by the solid line and the 95% confidence limits are indicated by the dotted lines (n = 108 eyes of 54 subjects).

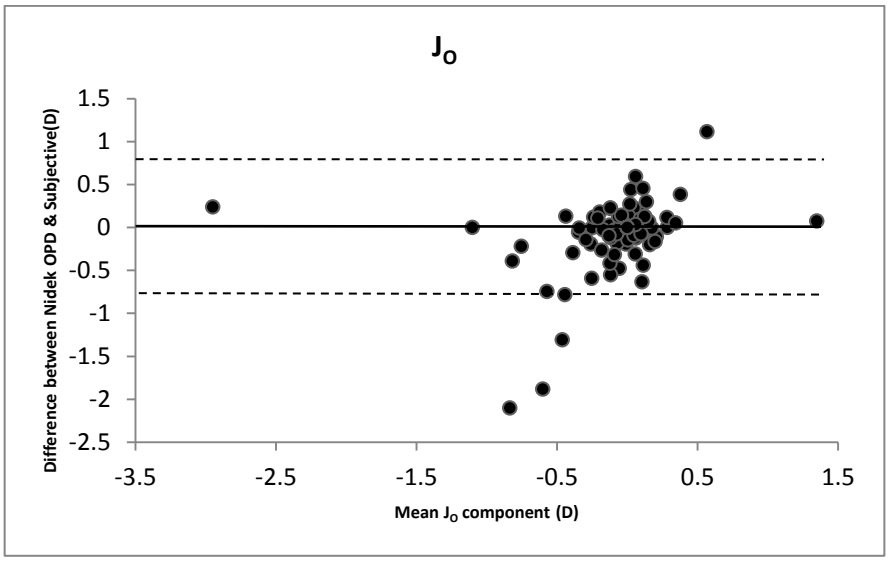
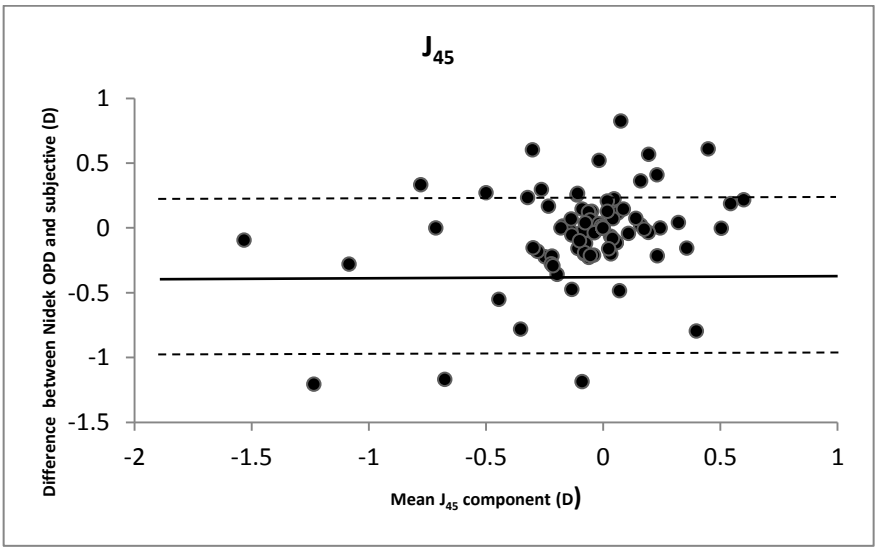


Figure 2.5 Difference in J_{45} cylindrical component between Nidek OPD-Scan III autorefractor and subjective refraction. The mean bias is indicated by the solid line and the 95% confidence limits are indicated by the dotted lines (n = 108 eyes of 54 subjects).



The oblique autorefractor cylindrical vector was slightly more negative (Figure 2.5), the mean difference between the Nidek OPD-Scan III and subjective refraction was -0.36 ± 0.31DC p = 0.86, the 95% LoA between the methods were -0.97 to 0.24DC. Approximately 93% of cylinder powers measured by Nidek OPD-Scan III were within ± 0.25DC and 96% within ± 0.50D. In terms of axis, 60% of all cylinders powers were within 5° and 84% were within 10°. For cylinders ≥ 0.75, 47% were within 5°, 89% were within 10° (Table 2.1).

The visual acuity was compared for both methods. The mean deviation was 0.01 ± 0.46 logMAR; p = 0.78. The 95% LoA between the methods were -0.89 to 0.91 logMAR.

The intra-test variability was small; the spherical component varied by 0.07DS, the mean spherical equivalent by 0.07DS, the cylindrical component 0.04DC, J_O 0.06DC and J_{45} 0.05DC. The inter-test variation was small and 90% of the sphere and cylinder

results were within ± 0.25DC (Table 2.2). The visual acuity was compared for both methods and the results are shown in Figure 2.6.

As the dioptric results from the two methods were generally in close agreement, the acuities reflect this, however, when the Nidek OPD-Scan III gave a different reading to the subjective, the visual acuities were the same or worse.

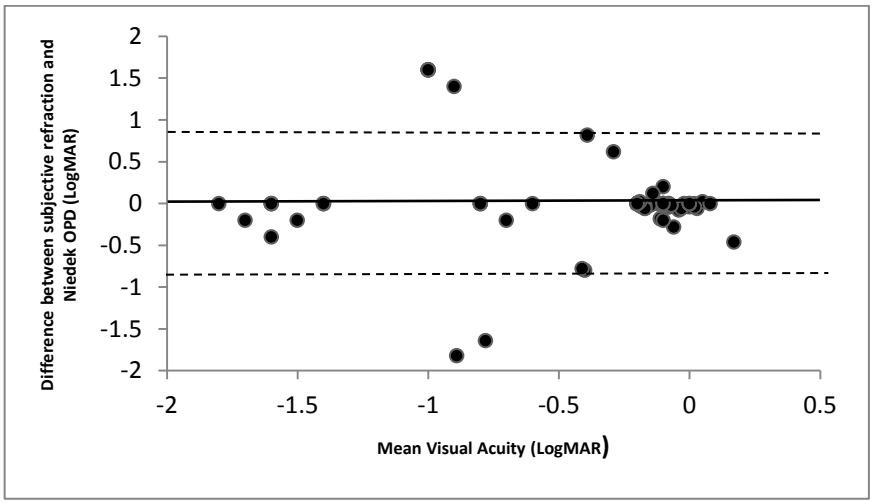
Table 2.1 Comparison of the axis of the cylindrical components between Nidek OPD-Scan III autorefractor and subjective refraction.

Difference in axis	**All prescriptions with a cylindrical component n=84**	**Prescriptions with a cylindrical component ≥0.75D n=21**
±5°	50 (60%)	10 (47%)
±10°	70 (83%)	19 (90%)
±15°	74 (88%)	19 (90%)
±20°	78 (93%)	20 (95%)

Table 2.2 Mean difference in refractive components between Nidek OPD-Scan III autorefractor and subjective refraction (n = 28) between different sessions (Inter-session repeatability).

Refractive component	**Mean Difference (DS or DC)**	**SD of differences**
Sphere	-0.07	0.24
Mean Spherical Equivalent (MSE)	-0.07	0.24
J_O	-0.06	0.25
J_{45}	0.1	0.29
Cylinder	0.01	0.25

Figure 2.6 Difference in corrected visual acuity between Nidek OPD-Scan III autorefractor and subjective refraction. The mean bias is indicated by the solid line and the 95% confidence limits are indicated by the dotted lines (n = 108 eyes of 54 subjects).



2.5 Discussion

The results for autorefraction were generally in close agreement with the subjective refraction results. Treating the subjective refraction as the 'gold standard', however, does have limitations (French, 1974), particularly as one practitioner performed all refractions. Repeated subjective refraction by one or a different practitioner may show larger spread in agreement (Goss and Grosvenor, 1996). The decision was taken to minimize errors which may be attributed to the individual clinician by allowing access to previous records and best corrected visual acuities. This also closely aligns with procedures in refractive practice and has been used elsewhere (Pesudovs and Weisinger, 2004).

Jorge et al. found retinoscopy rather than autorefraction to be the best starting point for experienced clinicians conducting non-cycloplegic refraction (Jorge et al., 2011).

Jinabhai found aberrometry to be superior to subjective refraction in keratoconic eyes, particularly those which were highly aberrated (Jinabhai et al., 2010).

The bias results for spherical and mean spherical equivalent (Spherical -0.19DS; MSE -0.19DS) were small in line with other studies, which ranged from spherical 0.04DS; MSE 0.01DS (Sheppard and Davies, 2010) to spherical 0.18DS; MSE 0.14DS, (Davies et al., 2003a), however, a greater number of prescriptions fell within ±0.25DS than with any other study (Mallen et al., 2001, Shneor et al., 2011, Sheppard and Davies, 2010, Davies et al., 2003a, Kinge et al., 1996).

Generally there was little difference between the subjective and objective techniques and no trend across the age ranges, with results for the 5 year old subject within 0.25 for the techniques (more negative for autorefraction).The slight negative bias for the spherical component and particularly the hyperopic outlier may be linked to the fact that the instrument is a closed field autorefractor, although it does use an 'auto-fogging' function to control accommodation. Overcoming the effects of accommodation is crucial for accurate refraction (Suryakumar and Bobier, 2003, Zhao et al., 2004, Choong et al., 2006) and therefore it may be useful to assess more young hyperopes with this instrument to determine if this was an unusual result. Fincham showed that changing the vergence of light at the retina in a young subject initiated a reflex change in accommodation and that accommodation was particularly stimulated by chromatic aberration of the eye and scanning (Fincham 1951). In a closed-field autorefractor, the image is coloured and it is possible for the subject to scan around the image, despite the auto-fogging mechanism. Therefore this could potentially be a reason for this anomalous result, as it was not possible to control for accommodation in this case.

In terms of cylindrical components, the bias of -0.002DC was less than other studies, although all values were low e.g. 0.01DC (Sheppard and Davies, 2010) and 0.05D (Shneor et al., 2011). The values for J_0 were comparable; however, the bias of 0.36DC

for J_{45} was more than reported in similar studies (0DC, (Sheppard and Davies, 2010) -0.005DC (Shneor et al., 2011)). The agreement between methods for cylinder power and axis was comparable to Shneor (87% within ± 0.25DC, 97% with ± 0.50DC (Shneor et al., 2011).

The intra-session repeatability was comparable with other studies (Mallen et al., 2001, Shneor et al., 2011, Sheppard and Davies, 2010, Davies et al., 2003a, Cleary et al., 2009) inter-session repeatability of 90% within ± 0.25D for sphere and cylinder was better than reported by any previous studies, the closest being Shneor with 80% and 91%, respectively (Shneor et al., 2011). Sheppard and Davies (2010) reported a slight myopic bias for all prescription elements on re-testing using an open-field autorefractor, however, Schneor (2011) found a positive bias, which they attributed to a hyperopic outlier. Small fixation instabilities are difficult to control and closed field autorefractor manufacturers attempt to correct for accomodation using fogging techniques and distance scenes as targets (Strang 1998). Microfluctuations in accommodation (small oscillations in the power of the lens of between 0.03-0.50D) (Charman 1988) can be problematic in autorefractor measurements as refraction is measured over a very short period, although some allowance for this can be made by averaging. The acquisition time is approximately 400mS in the Nidek OPD-Scan III, which is longer than most Hartmann-Shack based systems (Montés-Micó 2008) and therefore may explain why the results were slightly more repeatable than most studies.

The limitation for this study is the accuracy of the statistical findings given the correlation for measurements obtained from the right and left eyes of a subject. Careful consideration was given as to whether it was advantageous to collect data from both eyes and the decision was taken to use the same statistical technique as the most recent previous paper (Schneor et al. 2011). The risk of this strategy was the violation of the assumption of independence of the data as the variation between eyes is usually less than between subjects, therefore leading to an underestimation of the true

variance and risking falsely rejecting the null hypothesis (that there is no difference between the measures) when it is in fact true. Alternative and more accurate strategies would have been to use the data from both eyes and allow for the correlation between the two eyes using an intraclass correlation coefficient, or randomly including one eye of each subject (Armstrong 2013).

2.6 Conclusion

The Nidek OPD-Scan III is a compact, multi-function instrument with a clear touch-screen interface. The combination of measurement facilities allows rapid assessment of a range of ocular parameters for use in research and clinical practice. It is reliable, accurate and easy to use, although the refraction results may often require small modifications in many cases for prescribing purposes. In the case of young hyperopes, the results show further investigation may be required, possibly using cycloplegia, which may yield more accurate measurements.

2.7 Summary

This chapter introduced the Nidek OPD Scan III and demonstrated that it is reliable and accurate when measuring lower, second radial order aberrations. Chapter 3 will develop the concept of objective measurement of aberrations and the Nidek OPD-Scan III will be used to quantify higher order aberrations in normal and dry eyes following application of lubricants.

Chapter 3 - THE IMMEDIATE EFFECT OF OCULAR LUBRICANTS ON HIGHER ORDER ABERRATIONS AND SELF-REPORTED COMFORT IN NORMAL AND DRY EYE

3.1 Introduction

The previous chapter demonstrated that the Nidek OPD-Scan III is accurate as an autorefractor. The role of the aberrometer extends beyond this basic characterisation of refractive error, however, as wavefront sensing can be used to link the visual performance of an eye to specific defects in the eye's optics**.** Conventional measures of visual performance e.g. Snellen acuity or contrast sensitivity do not make this link. Aberrometry has been used to examine the relationship between refractive error and monochromatic aberrations of the eye; higher order aberrations were uncorrelated with refractive error in myopia or hypermetropia, however, astigmatic eyes demonstrated a higher value for total higher order aberrations than non-astigmatic eyes (Cheng et al., 2003). Keratoconic eyes exhibit high levels of aberrations and aberrometry has allowed objective and quantitative assessment of the optical outcome of penetrating keratoplasty (Munson et al., 2001). Similarly, aberrometry has been used to investigate visual quality in refractive laser surgery (Mrochen et al., 2001, Moreno-Barriuso et al., 2001, Oshika et al., 1999), contact lenses (Lu et al., 2003, Hong et al., 2001, Dietze and Cox, 2003), intraocular lenses (Guirao et al., 2002, Bellucci et al., 2003, Bellucci et al., 2005) and dry eyes (Tutt et al., 2000, Montés-Micó et al., 2004b). This chapter shows the use of the Nidek OPD-Scan III as an aberrometer to measure higher order aberrations in normal and dry eyes.

3.2 Analysis of wavefronts

Wavefront aberrations can be thought of as the difference between a wavefront reflected from a point surface on the retina and an ideal reference wavefront (Thibos, 2001). The most common type of algorithm used to analyse and describe wavefront

aberrations is a system developed by Fritz Zernike. He developed a set of orthogonal mathematical functions (polynomials) consisting of shapes of growing complexity combining to describe a surface that fits as closely as possible to a measured wavefront. The wavefront error is measured as a discrete set of points along the wavefront, enabling the shape to be calculated. This shape is expressed as the square root of the mean of the square of the wave aberrations across the pupil aperture or the root mean square (RMS), measured in micrometres (μm) (Thibos et al., 2002a). The 'wavefront maps' use colour gradients to represent the powers of the aberrations and can be displayed as a pyramid in a systematic classification, starting from radial order 0 (piston), radial order 1 (tip and tilt) and can be drawn to whatever radial order is required (Wang and Koch, 2003). This system was first used to describe aberrations in human eyes in 1977 by Howland and Howland (Howland and Howland, 1977). The first order modes are the linear terms, tip and tilt, which are equivalent to vertical and horizontal prism and do not affect image quality under monochromatic conditions (the effects of dispersion have to be considered in polychromatic systems). The second order can be corrected by spectacles or contact lenses and are the quadratic terms, defocus (sphere) and cylinder (astigmatism). The third order modes represent coma and coma-like aberrations. The fourth order contains spherical aberration as well as other modes. The fifth to tenth orders are the higher order, irregular aberrations. Terms from the third order (coma and trefoil) and fourth order (spherical aberration and trefoil) are the most prevalent in the human eye. For most Zernike modes, the aberration coefficients are symmetrically based around zero, however, spherical aberration is systematically biased towards positive values (Thibos et al., 2002b). Higher order aberrations reduce retinal image contrast in the visible range of spatial frequencies and increase with pupil size e.g. in a 7.3mm pupil at 20 cycles per degree (cpd), the retinal image contrast can be reduced by a factor of 7 (Liang and Williams, 1997). The aberrations tend to be symmetrical in left and right eyes of the same observer and the highest mean values have been shown to be fourth order spherical aberration, third

order coma and trefoil terms, respectively. The visual impact of the same amount of RMS aberration is not the same for all Zernike modes (Applegate et al., 2003a) and the effects of different modes may interact so that sometimes the combined effect of two aberrations degrades visual performance to a smaller extent than either, when considered separately (Applegate et al., 2003b). In most normal eyes, modes above the fourth order only have a minor effect on the retinal image for pupil diameters of 6mm (Porter et al., 2001), although coefficients increase rapidly beyond 4mm (Charman, 2005).

Figure 3.1 Illustration of Zernike polynomials up to the fifth order (http://www.clspectrum.com/articleviewer.aspx?articleid=101060; accessed 27 June 2013).

Fourier analysis can also be used to analyse wavefronts. Jean Baptiste Fourier was a French professor of mathematics, who showed that any repetitive waveform can be broken down into a series of component waves, in a similar sense to analysing which chemicals make up a complicated compound. In a complicated wavefront it is possible to calculate how many sines and cosines make up the signal and what their amplitudes

are. For a given Fourier coefficient, it is possible to identify which frequencies are present in the signal and in what quantities. The Fourier system can accurately describe even the most complex wavefronts with no smoothing of the data, unlike in Zernike polynomials. Klyce et al. concluded that Zernike polynomials did not capture all the clinically significant data in highly complex waveforms, such as those found in eyes with ocular surface disease (Klyce et al., 2004). Zernike polynomials are also pupil size and shape dependent as they only describe aberration in a round aperture; oval pupils will have peripheral data points which are not described. One of the main reasons why Zernike polynomials remain popular and have been used within this current study, however, is the familiarity of the terms and the clear representation of the 3-dimensional surface by the series of pre-determined 'best fit' shapes. With Fourier analysis, the visual system is split into individual terms and although each point is individually analysed, the analysis gives more complex results, which make clinical correlations difficult to make.

The Strehl ratio is a metric for retinal image quality and gives an indication of how much the image quality could be corrected. The Strehl ratio is the ratio of the peak intensity of the eye's point spread function to that of a point spread function for an aberration free eye with the same pupil size in which diffraction is the only source of blur (Iskander 2000).

3.3 Ocular aberrations following instillation of artificial tears

Montés-Micó investigated the effect of artificial tears on aberrations in dry eye and found significant decreases in optical aberrations, particularly of coma and spherical aberrations (Montés-Micó et al., 2004a). The improvement in visual quality was indicated by the point spread functions and the effects of the artificial tears were still apparent ten minutes later. Aberrometry was then used to compare the performance of optical lubricants with different viscocities in healthy eyes (Berger et al., 2009),

however, there was criticism over the lack of consideration regarding pH and osmolarity of the preparations, which may have impacted on the results (Chen et al., 2009).

Lin et al. investigated the effect of tear-film break up on higher order aberrations and found a significant increase in aberrations in normal and dry eyes from post-blink to the tear break up and a decrease in aberrations after instillation of saline in coma, trefoil and from 3rd through to 6th order aberrations. It was concluded that the disruption of the tear film increased anterior corneal higher order aberrations in normal eyes and this effect was more rapid in dry eyes (Lin et al.). Long term use of artificial tears in dry eyes have been shown to normalize the tear film in dry eye, reducing higher order aberrations and improving contrast sensitivity (Ridder III et al., 2009). Tung used wavefront sensing and optical coherence tomography to compare the optical quality in dry eyes following instillation of different drops. Worse visual quality was recorded in subjects with more severe dry eye, regardless of drop type, and there was a correlation shown between tear meniscus dimensions and visual quality to the point where the visual quality got worse with excessive tear volume (Tung et al., 2012), echoing the findings of Koh et al. when investigating the effect of punctual occlusion in mild dry eye (Koh et al., 2006b). Limitations to all studies investigating lubricants include a lack of standardisation in defining dry eye subjects and differing severity of dry eye in subjects within and between studies. The lack of standardisation in drop size, varying osmolarity and viscosity of drops and the use of dilating drops or anaesthesia can all confound the results. Studies comparing different groups of individuals rather than using an individual as their own control are more prone to error as physical characteristic e.g. lid position or blinking habits (McMonnies, 2007) may be different between the groups.

Aberrometry is a useful method to assess the tear film and ocular surface. It cannot define the cause or type of dry eye; however, it can give valuable information about the refractive properties of the anterior cornea and tear film. Perhaps more importantly, it

provides objective information about the consequences for visual performance of any intervention.

3.4 Study aim

The purpose of this study was to examine the effects of unpreserved hypromellose 0.3% w/v artificial tears (Lumecare®, Medicom Healthcare Ltd, Hampshire, UK) a liposome spray (Tears Again®, Optima Pharmazeutische GmbH) and the treatments combined, on patient-reported ocular comfort, higher order aberrations and Strehl ratio in normal and self-diagnosed dry eye subjects.

3.4.1 Sample size

The Power calculation was conducted using G*Power 3.1 (Faul et al., 2007) (ANOVA repeated measures within factor). The sample size was determined based on previous data from Craig et al. (2010), NIBUT at baseline (13.1 ± 8.8s) and 60 minutes (22.0 ± 12.2s). A total of 48 subjects; 24 with normal eyes and 24 subjects with self-diagnosed dry eyes were required to achieve 80% power and an alpha level of 0.05. Twenty seven were recruited for each group to allow for drop out.

3.4.2 Subjects

The study was approved by the institutional ethics committee and the research followed the tenets of the Declaration of Helsinki. The nature of the study was explained to the participants and written, informed consent was obtained. The inclusion criterion for dry eye was a score of ≥6 according to the Chalmers 5-item questionnaire (Appendix 1) (Chalmers et al., 2010). The mean dry eye questionnaire score for the normal group was 2.7 (median 2, SD 2.3). The mean dry eye questionnaire score for the dry group was 10.7 (median 12, SD 3.2). The exclusion criteria were: diagnosis of dry eye or any eye disease including ocular allergy, medication affecting the ocular

surface, refractive surgery, contact lens wear and use of any eye drops within 24 hours prior to the study.

The measurements were conducted in a stable, air-conditioned environment of 21°C and 24% humidity. Subjects remained in this environment between measurements, during which time they performed tasks requiring high levels of concentration.

3.4.3 Experimental procedure

The subjects were assessed for all interventions administered to the right eye only on three different days within a two week period. The interventions were one drop of unpreserved hypromellose, one spray of liposome solution and the drop and spray combined. Unpreserved drops were selected as common preservatives e.g. benzalkonium chloride have a detergent effect (Baudouin et al., 2010) and the potential effect of this detergent on the liposome spray was unknown. Allocation of treatment order was decided for each subject using randomisation tables. Comfort levels for the right eyes were rated on a scale of 1-10, where 10 represented the most comfortable at baseline and after 1 hour. The subjects were seated with their chin on the chin-rest of the aberrometer when any lubricants were applied to enable the investigator to measure aberrations 5 seconds after intervention. Aberrometry was performed 2 seconds after a blink (aberrations are stable for up to 4s after a blink (Thai et al., 2002) at baseline, 5 seconds after treatment and 1 hour after treatment using the Nidek OPD-Scan III. The total eye wavefront error, total spherical aberration and total coma-like aberrations were recorded over a pupil diameter of 5mm, as this was the smallest natural pupil size in this cohort. Coma and spherical aberrations have been shown to have the most significant effect on visual quality (Salmon and van de Pol, 2006). Magnitudes of the coefficients of Zernike polynomials were represented as the root mean square (RMS, in micrometres). The Strehl ratio for higher order aberrations was also recorded as a predictor of the optical quality at the fovea, higher values indicating

improved image quality (Iskander et al., 2000). A slit-lamp examination was performed after the final aberrometry reading to assess corneal staining using fluorescein sodium. The hypothesis for this study was that the combination of aqueous drops and a liposomal spray would result in the most stable and improved optical surface in the dry eye group after 60 minutes. The normal group was expected to exhibit minimal change after 60 minutes.

3.4.4 Randomisation

Allocation of treatment order was decided for each subject using randomisation tables (generated by http://www.randomizer.org/form.htm).

3.4.5 Statistical analysis

Statistical analysis was performed with SPSS v20.0 (SPSS INC., Chicago, USA). The ranked data was analysed using Friedman's ANOVA, with post hoc Bonferroni corrected Wilcoxon signed-rank tests. Normally distributed continuous data underwent parametric statistical analysis. Normality was confirmed for the data sets using Kolmogarov-Smirnov, $p > 0.05$. Analysis of variance (ANOVA) or 2 tailed independent t-tests were used to analyse the data. When ANOVA results were significant, post hoc Bonferroni corrected t-tests were used to control for Type 1 error. A 'p' value of less than 0.05 was considered significant.

3.5 Results

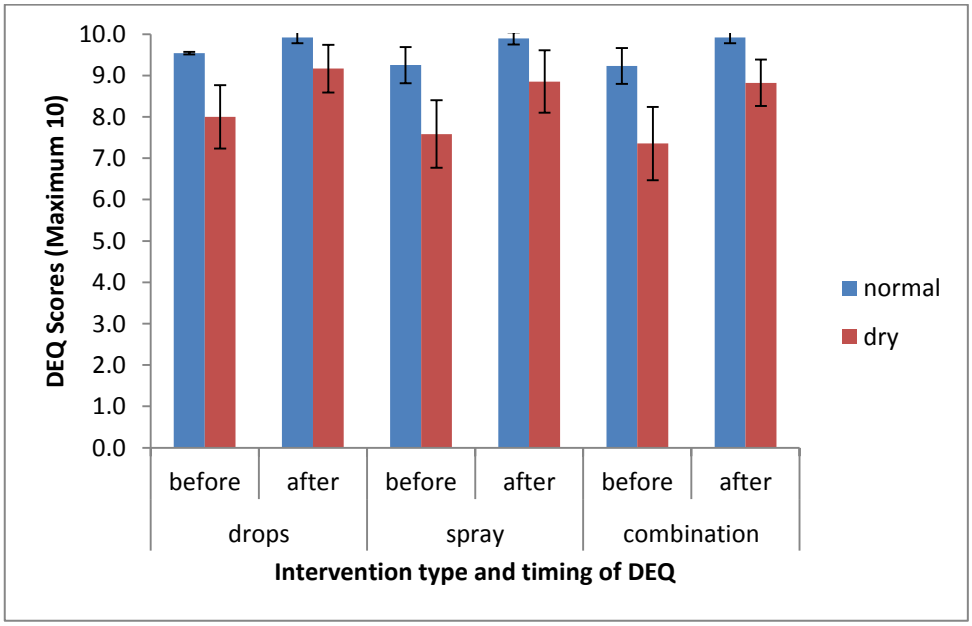
The results for 24 subjects with normal eyes (12 female, 12 male) with a mean age of 24.2 (SD 8, median 21) years and 24 subjects with self-diagnosed dry eye (15 female, 9 male) with a mean age of 25.7 (SD 7, median 22) years were included. The comfort scores revealed the largest improvement after the combination treatment; χ^2 (2) = 6.240 $p = 0.04$ (Mean improvement in normal eyes 0.7 ± 0.2 and dry eyes 1.4 ± 1.1), followed by spray (Mean improvement in normal eyes 0.6 ± 0.2 and dry eyes 1.3 ± 1.3)

then drops (Mean improvement in normal eyes 0.4 ± 0.2 and dry eyes 1.2 ± 1.1). The scores had larger standard deviations in the dry group, although post hoc comparisons between specific interventions and eye types did not reach statistical significance and the comfort scores did not support the treatment preferences (Figure 3.2).

Table 3.1 Treatment preferences for all subjects (n = 24 for each group).

Treatment		**Hypromellose drops**	**Liposome spray**	**Combination**	**No preference**
Subjects	Normal	66.60%	33.40%	0	0
	Dry	37.60%	50%	8.40%	4%

Figure 3.2 Comfort scores out of 10, before and one hour after treatment (n = 24 for each group), where 10 represents the most comfortable (SD indicated).



The baseline total higher order aberrations, coma and spherical aberrations between the normal and dry groups were investigated to determine if there was a change in values across the visits before any intervention. The mean values for total higher order aberrations were slightly higher in the dry group; however, the standard deviations

were large and this did not reach statistical significance on any separate occasion (Table 3.2).

A mixed ANOVA model (eye type X time of measurement) was designed to determine whether the Strehl ratio for higher order aberrations showed a reduction by similar amounts in normal and dry eyes at each measurement time point. The Strehl ratio was reduced by similar amounts in normal and dry eyes immediately after instillation of hypromellose drops. Bonferroni corrected post hoc tests showed this related to the change from baseline to immediately after instillation of hypromellose drops (mean difference 0.39, $p<0.01$ and 0.36, $p = 0.01$ for normal and dry eyes respectively) and immediately after instillation versus an hour after instillation (mean difference -0.42, $p = 0.01$ and -0.23, $p = 0.04$ for normal and dry eyes respectively). There was no significant effect for eye type or time of measurement when assessing Strehl ratio for application of spray alone ($F\ 2, 92 = 1.90$, $p = 0.16$) or for the combination of drops and spray ($F\ 2, 92 = 0.542$, $p = 0.59$). Tables 3.3, 3.4 and 3.5 show the objective values and standard deviations for normal and dry eyes at baseline and 60 minutes after intervention. For the hypromellose drops there was a significant main effect for the time of measurement, $F\ (2, 92) = 9.91$, $p = <0.01$; Bonferroni corrected post hoc tests showed this related to the change from baseline to immediately after instillation of hypromellose drops (mean difference in normal eyes 0.130, $p = <0.01$; mean difference in dry eyes 0.036, $p = 0.01$), however there was no significant difference between measurements taken at baseline and an hour after intervention in either eye type. For liposome spray there was no significant effect for time of measurement, $F\ (2, 92) = 1.905$, $p = 0.155$ or eye type, $F\ (1, 46) = 1.839$, $p = 0.18$. For hypromellose drops and liposome spray combined there was no significant effect for time of measurement $F\ (2, 92) = 0.529$, $p = 0.60$, or eye type $F\ (1, 46) = 0.911$, $p = 0.35$.

Table 3.2 Results of independent t-test for baseline total higher order aberrations between normal (n = 24) and dry (n = 24) eyes on each separate visit.

	Baseline visit Hypromellose Drops			**Baseline visit Liposome Spray**			**Baseline Visit Combination**		
	Normal Eyes	**Dry eyes**	**P value**	**Normal Eyes**	**Dry Eyes**	**P value**	**Normal Eyes**	**Dry Eyes**	**P value**
Coma (µm)	0.105 ± 0.045	0.100 ± 0.050	0.75	0.085 ± 0.042	0.106 ± 0.048	0.12	0.090 ± 0.056	0.104 ± 0.057	0.37
Spherical aberrations (µm)	0.044 ± 0.033	0.036 ± 0.022	0.34	0.041 ± 0.029	0.039 ± 0.029	0.87	0.040 ± 0.027	0.058 ± 0.078	0.36
Total higher order aberrations(µm)	0.218 ± 0.078	0.237 ± 0.078	0.29	0.204 ± 0.075	0.238 ± 0.063	0.14	0.213 ± 0.091	0.239 ± 0.084	0.21

Figure 3.3 Mean strehl ratio at baseline, immediately after instillation (After) and one hour after (Hour) instillation of drops, spray and the lubricants combined in normal (n = 24) and dry (n = 24) groups.

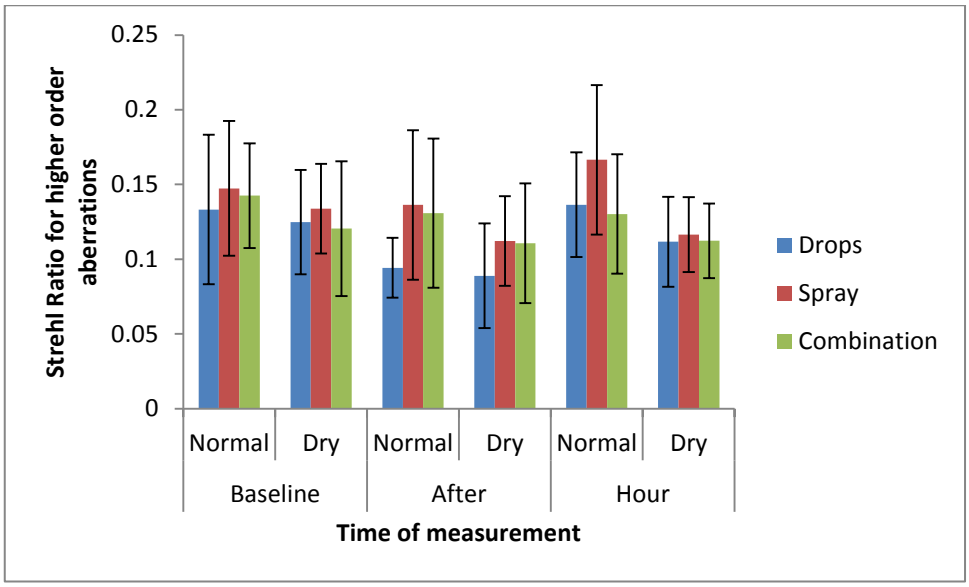
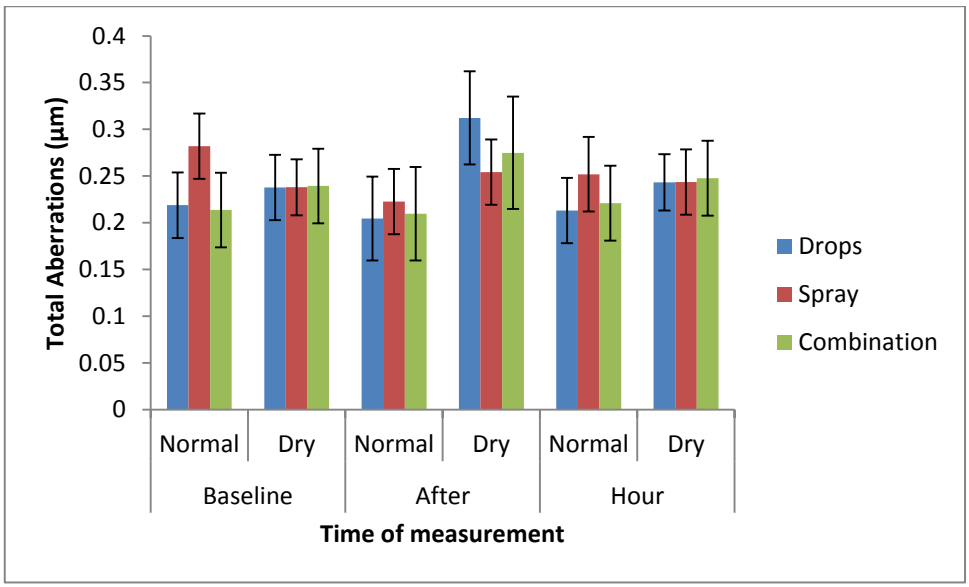
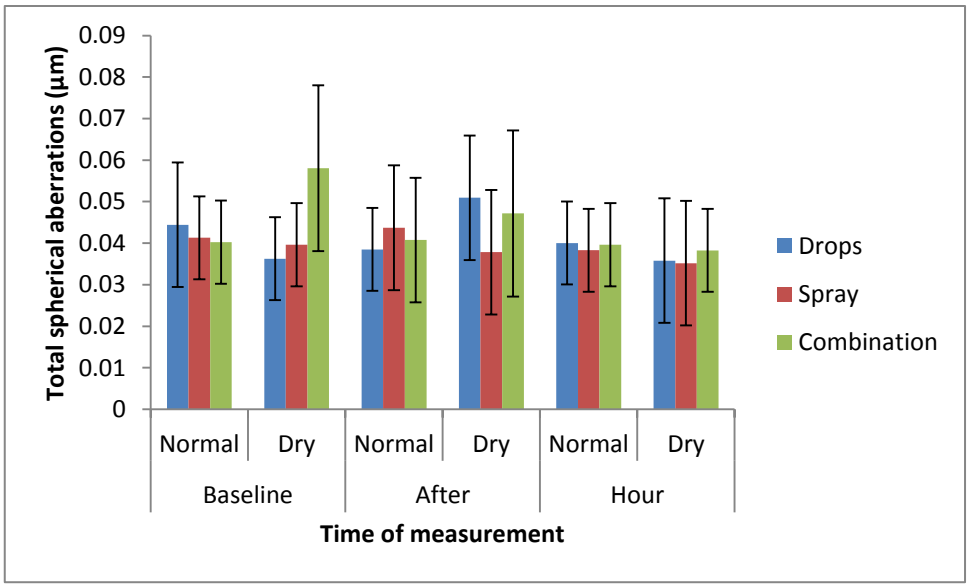


Figure 3.4 Mean total aberrations ratio at baseline, immediately after instillation (After) and one hour after (Hour) instillation of drops, spray and the lubricants combined in normal (n = 24) and dry (n = 24) groups.



Instillation of hypromellose drops increased total aberrations (F (1.36, 62.61) = 19.00, p<0.01, Greenhouse-Geisser corrected) from the 'baseline' compared with 'immediately after' (mean difference 0.23, p<0.01 for normal and dry eyes) and there was a similar sized reduction at the 'immediately after' compared with 'hour' time points (mean difference 0.22, p<0.01 for normal and dry eyes). There was no significant effect for eye type, F (1, 46) = 1.782, p = 0.19. Analysis for the effect of liposome spray on total aberrations showed no significant effect for time of measurement, F (2, 92) = 1.756, p = 0.18 or eye type, F (1, 46) = 3.060, p = 0.09. For drops and spray there was no significant effect for time of measurement F (2, 92) = 4.387, p = 0.15, or eye type F (1, 46) = 1.118, p = 0.30.

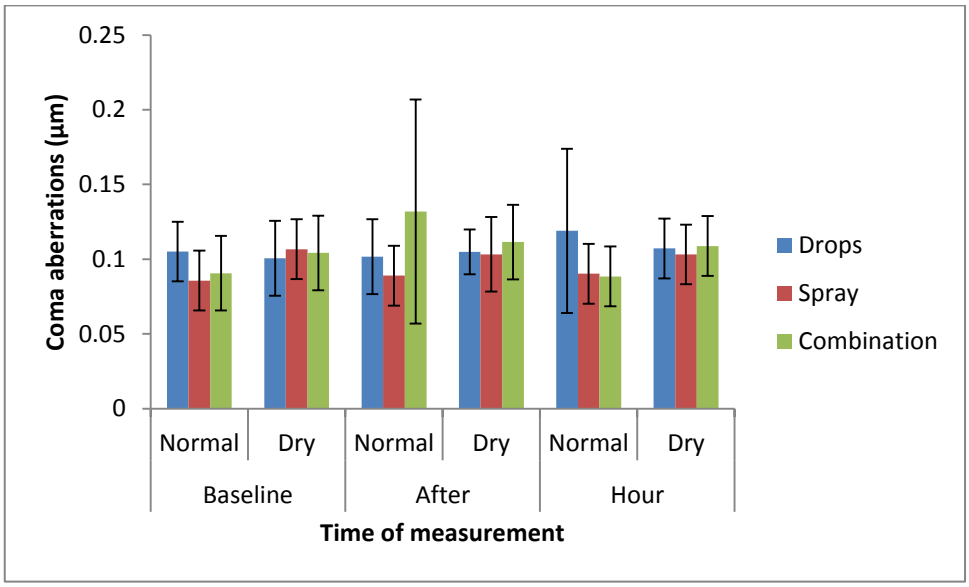
Figure 3.5 Mean spherical aberrations at baseline, immediately after instillation (After) and one hour after (Hour) instillation of drops, spray and the lubricants combined in normal (n = 24) and dry (n = 24) groups.



Instillation of hypromellose drops had no significant effect on spherical aberrations for time of measurement F (2, 92) = 1.282, p = 0.29 or eye type F (1, 46) = 1.112, p =

0.33. The main results for time of measurement after application of liposome spray were F (2, 92) = 1.112, p = 0.33, with no significant difference for eye type F (1, 46) = 1.112, p = 0.33. The effect on spherical aberrations for the interventions combined was insignificant; F (1.39, 63.77) = 0.836, p = 0.40, Greenhouse-Geisser corrected. There was no significant effect for eye type (F1, 46) = 0.781, p = 0.38.

Figure 3.6 Mean coma aberrations at baseline, immediately after instillation (After) and one hour after (Hour) instillation of drops, spray and the lubricants combined in normal (n = 24) and dry (n = 24) groups.



Instillation of hypromellose drops had no significant effect on coma for time of measurement F (1.49, 63.40) = 0.527, p = 0.54 or eye type F (1, 46) = 0.106, p = 0.74. The main results for time of measurement after application of liposome spray were F (2, 92) = 0.120, p = 0.89, with no significant difference for eye type F (1, 46) = 0.09, p = 0.77. The effect on coma for the interventions combined was insignificant; F (1.21, 55.52) = 1.767, p = 0.19, Greenhouse-Geisser corrected. There was no significant effect for eye type (F1, 46) = 0.071, p = 0.80.

3.6 Discussion

A third of the ‘dry eye’ group scored 7 in the questionnaire, which only just placed them in to the ‘dry’ category. There is a strong possibility that the differences between the ‘normal eye’ and ‘dry eye’ groups failed to reach statistical significance due to the high proportion of borderline ‘normal eyes’ in the ‘dry eye’ group. There were large standard deviations in all measurements of higher order aberrations, which would mean a much larger sample size would be needed to show an effect. The figures used for the calculation of power were based on previous studies with diagnosed dry eye and therefore they would be far less likely to have overlapping values for higher order aberrations. It is known that total higher order aberrations induced by flying spot laser surgery tend to be in the region of 0.25µm for a 6mm pupil (Applegate 2003) and this explains why there was very little reduction in visual quality in photopic conditions for any of the participants of this study. Koh et al. had previously shown that optical quality may deteriorate in borderline dry eye cases, even with sufficient tear volume, when gazing at a VDU. In this current study, we allowed natural blinking patterns, however, Koh et al. measured higher order aberrations sequentially for 30 seconds and allowed subjects to blink just once every 10 seconds, therefore almost certainly exceeding normal tear breakup times (Koh et al., 2008b). The measurement of visual quality immediately after instillation of hypromellose drops was found to be significantly worse, in agreement with other studies investigating artificial tears (Ridder III et al., 2009, Tung et al., 2012, Berger et al., 2009), however, the non-significant result following instillation of the hypromellose drops and liposome spray combined was unexpected. This may have been due to small variations in drop size or amount of spray applied, however, the same investigator (SM) applied all interventions in an attempt to standardise the dosage. Ridder et al. measured the drop weight in their study, but concluded that it was unlikely to affect the results (Ridder III et al., 2009), so this is unlikely to have been a major factor. The timing of the measurements after a blink was another possible source

of variation; however, the technique used followed established protocol (Ridder III et al., 2009). The results are more likely to have been influenced by the psychological factor of having two interventions at the same time, which may have led to increased blinking or lid squeezing, where excess volume of the drop could wash the liposome spray away. The comfort scores, however, were marginally higher for the combination of products; the subjects possibly perceiving a larger effect due to 'more' intervention, although this did not extend to the treatment preferences. The convenience of having a multi-use spray which needed no mirror to aid application was a factor commonly cited by subjects when choosing their preferred product. The non-significant post hoc tests following a significant result for the Friedman analysis of the comfort scores may indicate a Type 1 error; however, it is more likely that this reflects a lack of power, particularly in a small sample size where the differences between the normal eyes and dry eyes was small.

Larger differences in higher order aberrations may have been found over an increased pupil diameter (Liang and Williams, 1997), however, these measurements were meant to reflect visual effects in average indoor lighting conditions. The values obtained by different methods of aberrometry have been shown to vary with respect to values for deviations in wavefronts. The automatic 'averaging' function has also been cited as a source for error as this is not an indication of reduced variance between the measurements; therefore, recommendations for multiple separate measurements have been made (Rozema et al., 2006). The differences between the dry and normal group did not reach statistical significance at the hour time point for any of interventions and there were large standard deviations in the measurements. This may be due to fluctuations in accommodation (Atchison et al., 1995, He et al., 1998) or the variable nature of the aberrations themselves e.g. local aberrations at the border of the tear film breaking up where the slope would be steep; the complex nature of such aberrations would not be well described by Zernike modes. Acceptable tolerances for

measurement with aberrometry may also mean that the error exceeds the differences in total aberrations between the normal and borderline dry eyes (Rodríguez Pérez et al., 2006, Liang and Williams, 1997).

It is not unreasonable to expect the effect in borderline dry eyes to be shorter lived and a difference to show between the groups at the 60 minute time mark based on Craig's findings investigating normal eyes (Craig et al., 2010). It may have been more informative to take measurements more frequently, for example every ten minutes, to see if there was a point where there was a difference between dry and normal eyes, however, the study was designed to assess the benefit of combining treatments and specifically showing a difference between normal and dry eyes at the 60 minute time point, which would have been of clinical interest.

Fluorescein sodium was used to assess corneal staining following the final aberration measurements; however, there was no staining in any participants. Ideally it would have been better to assess the cornea before treatment, but this would clearly interfere with the results due to the established destabilising effect the drug has on the tear film and the invasive nature of the test. Other studies have assessed staining on a different day to measurement for inclusion criteria (Tung et al., 2012, Ridder III et al., 2009); however, due to the variable nature of the tear film, the method chosen in this study was considered to be the most effective representation of the ocular surface at the time of measurement. There is also ambiguity regarding what fluorescein staining actually represents and particularly whether it really gives a true representation of the integrity of the cornea (Morgan and Maldonado-Codina, 2009).

3.7 Conclusion

Combining artificial tear drop and liposome spray treatments for dry eye did not improve or prolong effectivity as measured by aberrometry over a 5mm pupil in dry or normal eyes. One application of any ocular lubricant gave a subjective improvement, although this could not be detected by aberrometry after one hour. This may suggest

that in a clinical setting, symptomatic patients with no corneal staining could benefit from ocular lubricants for symptomatic relief without a detrimental effect on their vision.

3.8 Summary

This chapter showed that visual quality measured using aberrometry was not significantly altered 1 hour after instillation of ocular lubricants in normal or borderline dry eyes. Chapter 4 will investigate the effect of refractive laser surgery on visual quality using aberrometry in combination with other techniques.

Chapter 4 – VISUAL EFFECTS AFTER REFRACTIVE SURGERY

4.1 Introduction

The previous chapter investigated the effect of the tear film on higher order aberrations in normal and dry eyes. This chapter will investigate the effects of reshaping the cornea on visual quality.

Refractive surgery is an option for correction of ametropia in patients who are unhappy wearing spectacles or contact lenses and may be considered a lifestyle choice for some individuals (Gupta and Naroo, 2006). Demanding professions, including the armed forces, emergency services, transport industry and some manufacturing industries often have mandatory minimum vision standards. There are frequently differences between vision standards for entry and retention of personnel, although permanent medical downgrading in the British military due to severe contact lens-related infection (Musa et al., 2010) is an example of the potential consequences following contact lens wear in unsuitable conditions. Refractive surgery could offer a solution, not just to existing personnel, but to potential candidates who are currently ineligible due to refractive error (Clare et al., 2010). The US navy have been evaluating the 'safety, efficacy, visual recovery and visual quality' of refractive surgery for twenty years, concluding that it is safe and effective for existing and new personnel, with particular benefit in cost saving for retention of aviators (Stanley et al., 2008).

4.2 Ablation procedures

Photorefractive keratectomy (PRK) was introduced in the 1980's and used an ultraviolet beam generated by an argon fluoride (ArF) excimer laser to irradiate the corneal stroma following epithelium removal to change the curvature of the cornea (Munnerlyn et al., 1988). It was only possible to treat myopia and results for errors greater than -4.00 dioptres were unpredictable (Ficker et al., 1993). Early PRK procedures used small ablation zones. This combined with corneal haze produced

starbursts and halos around lights at night due to myopic blur circles. The magnitude of the halo was less with 5mm than 4mm zones (O'brart et al., 1994). The depth of ablation correlated with the loss of refractive correction and increased anterior stromal haze (Gartry et al., 1992) and there was severe postoperative pain and slow visual recovery.

This led to the introduction of laser in situ keratomilesis (LASIK) which had a much shorter visual rehabilitation, higher predictability, minimal postoperative discomfort and absence of corneal haze (Shortt et al., 2006). LASIK involves the use of a microkeratome or femtosecond laser to create a corneal flap which is replaced after laser ablation (Pallikaris et al., 1990). Reports of stromal flap displacement following a blunt injury have been reported many years after LASIK (Holt et al., 2012), particularly with temporal hinge placement (Galvis et al., 2013). Night vision and dryness symptoms have been recorded in significant numbers of patients (Bailey and Zadnik, 2007).

Although initially the risks associated with LASIK were thought to be low (Perez-Santonja et al., 1997), postoperative flap-related complications and corneal ectasia led to the development of modified surface ablation procedures such as laser-assisted subepithelial keratectomy (LASEK) and epithelial laser in situ keratomileusis (Epi-LASIK). LASEK uses dilute ethanol to create an epithelial flap which is replaced after the corneal stroma is ablated by laser. This technique has particular application for patients who have thin corneas or who are predisposed to trauma e.g. military personnel and athletes (Azar et al., 2012). Epi-LASIK differs in that the separation of the epithelial sheet is obtained mechanically without requiring the preparation of the cornea with alcohol or another chemical agent. A study comparing post-operative pain found epi-LASIK patients had significantly less pain in the first two hours and the best 1-day visual acuity; however, there was a high rate of flap failure and conversion to PRK (O'Doherty et al., 2007). Camellin et al. considered the advantages of adding an

alcohol solution to the epi-LASIK procedure with particular reference to flap-making, haze and pain. The addition of alcohol was thought to contribute to better flap and hinge creation, with the added benefit of less post-operative astigmatism and irregularities without increasing post-operative pain or haze (Camellin and Wyler, 2008).

Despite the fact that refractive surgery has been performed on millions of patients, the long-term safety and efficacy of the procedures is still of concern to patients and clinicians. The biomechanical strength of the cornea is compromised by surgical tissue extraction, although this tends to be more common in eyes with thinner corneas and higher myopia requiring greater laser ablation (Baek et al., 2001). A Cochrane report comparing PRK and LASEK found no clear evidence supporting LASEK over PRK (Li et al., 2012). A study comparing postoperative visual outcomes and complication rates between LASIK and LASEK found that LASEK induced less higher order aberrations than LASIK where total HOA and vertical coma were significantly greater (Kirwan and O'Keefe, 2009) and was probably superior for customized ablation (Dastjerdi and Soong, 2002).

Technical advances and improved understanding of the healing response (Mohan et al., 2003) have improved predictability, accuracy, efficacy, safety and stability of refractive surgery (Shah et al., 2012, McAlinden et al., 2011). Most excimer laser platforms use a 193 nm wavelength light to modify corneal shape as it is strongly absorbed and provides precise corneal tissue removal with little collateral damage (Trokel et al., 1983). Lembares et al. proposed that toxic excimer lasers could be replaced by solid-state laser systems following their demonstration of ‘a window of ablation’ between 220 and 190 nm (Lembares et al., 1997). Ren et al. had previously shown that solid state lasers created a smooth ablation surface and similar histopathological findings to excimer systems (Ren et al., 1994). Corneal hydration is often controlled during surgery by the topical application of balanced saline solution

(BSS) and removal of excess surface fluid. There is some controversy (Seider et al., 2013) over the effects of corneal hydration (Dougherty et al., 1994) and environmental humidity (Walter and Stevenson, 2004) in excimer platforms, however, the 213nm wavelength has a long penetration depth of BSS compared with 193 nm and may require less monitoring of corneal surface fluid during procedures (Dair et al., 2001).

Larger spot diameters in traditional excimer laser systems have been linked with mechanical stress on the cornea (Krueger et al., 2001); increasing cellular changes to corneal collagen (Kermani and Lubatschowski, 1991). The Pulzar Z1 solid state refractive laser (CV Laser Pty Ltd., formerly Custom Vis Laser Pty Ltd) (http://www.customvis.com/assets/media/brochure.pdf accessed 24/6/2013) has a neodymium:YAG diode pump laser source and generates a 0.6mm Gaussian-shaped flying spot approximately one third smaller than commonly used excimer platforms, e.g. Allegretto and Ladarvision (Shah et al., 2012), although the recently introduced Amaris (a flying spot excimer laser) has minimum beam size of 0.54mm (Kermani and Lubatschowski, 1991, McAlinden et al., 2011). The eye is tracked using the position of the limbus, iris pattern and limbal blood vessels as references and the patients gaze is tracked to control for potential changes in fixation.

Previous solid-state platform studies using PRK (Anderson et al., 2004, Roszkowska et al., 2006, Tsiklis et al., 2007b), LASIK (Tsiklis et al., 2007a) and LASEK (Shah et al., 2012) have shown comparable outcomes to excimer laser ablation in standard and wavefront guided procedures, although follow-up is currently limited to 6 months following LASEK and 1 year following LASIK and PRK.

Piñero et al. evaluated aberrometry outcomes in 60 eyes of 34 patients with low to moderate myopia following LASIK performed with the Pulzar Z1 solid-state laser. They found statistically significant increases in total higher order aberrations, primary coma and primary spherical aberrations, although the postoperative values were still within

the physiological range in the normal population (Piñero et al., 2012). The aberrometry outcomes of LASEK performed with a solid state laser have not currently been assessed.

4.3 Assessment of potential candidates for refractive surgery

Refractive surgery is an elective procedure, therefore careful assessment, including whether the patient is psychologically fit is paramount. General health contraindications include autoimmune diseases e.g. systemic lupus erythrematosus, pregnancy, diabetes (where there is retinopathy) and epilepsy (the patient must remain still during the procedure). A history of herpetic keratitis or active ocular infection/ inflammation would preclude surgery, however, a history of glaucoma or eye trauma may not be absolute contraindications. The ophthalmic surgeon has to consider each case history in combination with the clinical findings (Sakimoto et al., 2006).

All tests indicated during a routine eye examination are performed, including cycloplegic refraction, binocular vision assessment and full slit-lamp examination of the corneal surface and tear film quality. The Nidek OPD-Scan III is useful for pupillometry as mesopic values are given in addition to wavefront measurements. Maximum pupil size may have an implication for the likelihood of glare and halos following the procedure (Lackner et al., 2003, Dick et al., 2005), although this opinion has been disputed (Schallhorn et al., 2003). Pachymetry can be measured using ultrasound, although difficulty centring the probe on the thinnest part of the cornea may lead to larger measurements when compared with optical methods (Rainer et al., 2004). Optical methods are required to map the differences between the anterior and posterior surfaces, displayed as a pachymetry map which is important when considering irregularities of shape consistent with ectastic disorders such as keratoconus, pellucid marginal degeneration and forme fruste keratoconus (Sakimoto et al., 2006).

4.4 Oculus Pentacam topography system

The Pentacam (Oculus, Wetzlar, Germany) is a system which utilizes rotating Scheimpflug imaging to scan and measure the cornea and anterior chamber. A rotating Scheimpflug camera and a monochromatic blue LED slit light source (475 nm) rotate together 180° around the optical axis of each eye and acquires 25 images within 2 seconds. The images contain measurement points from the front and back corneal surfaces and the data is used to create axial and tangential maps. In the automatic release mode, the instrument automatically determines when correct focus and alignment with the corneal apex have been achieved and then performs a scan. In less than 2 seconds, the rotating camera captures up to 50 slit images of the anterior segment, while minute eye movements are captured by a second camera and corrected simultaneously. Each slit image consists of 500 true elevation points. Mathematical software is used to detect edges in each slit image, including the epithelium and endothelium of the cornea, and a 3-D mathematical model of the anterior segment is constructed. The anterior surface of the cornea is calculated with no optical distortion and according to the manufacturer; the tear film has no effect on measurements. Each successive layer, such as the posterior corneal surface and anterior lens surface is calculated by ray tracing, with the calculation taking into account optical distortion. Single-point pachymetric measurements of the entire cornea are calculated from the calculated front and back surfaces. Since the centre of the cornea is measured repeatedly during the rotational imaging process (in each of the images), very precise determination of central corneal thickness can be achieved. The device has been shown to have a high degree of reproducibility and central corneal thickness values were closer to values obtained using ultrasound than Orbscan (Bausch and Lomb, Rochester, NY, USA) which is a scanning-slit device (Lackner et al., 2005).

4.5 Visual field changes following refractive laser surgery

Montés-Micó and Charman used a Goldmann perimeter (Goldmann perimeter 940, Haag-Streit AG) to assess visual fields in PRK subjects, revealing significantly poorer thresholds from 40-60° in comparison to natural emmetropes, which they attributed to the size of the ablation zone, blending zone, the desired optical correction and pupil size. They also suggested that diagnostic or therapeutic procedures carried out in the periphery, particularly imagery, may be affected by these optical effects (Montés-Micó and Charman, 2002). Charman then used modified model eyes (based on Navarro's finite schematic eye) to calculate the peripheral image effect on a myopic eye following PRK. He theorised that with a 6.0mm central ablation zone and 5mm pupil, the blur effect would start to occur at 15°, with increases in pupil size bringing blur effects closer to fixation, although this could vary depending on the transition zone (Charman et al., 2002). Ma et al. suggested the transition zone would be involved for angles of 25-30° in myopic or hyperopic LASIK patients with a 3mm pupil and ablation diameter of 5.5-6mm (Ma et al., 2005). Case studies of visual field changes following LASIK have shown ring scotomas, one attributed to optical effects (Brown and Morales, 2002) and a more ambiguous case where it was difficult to distinguish whether the defect was due to the laser procedure or glaucomatous loss (Austin et al., 2006).

4.6 Visual field assessment using Humphrey automated perimeter

The Humphrey automated perimeter uses stimuli equivalent to a Goldman size III target over a range of 51 decibels projected onto a bowl area with a background illumination of 31.5 apostilb (Heijl and Patella, 2002). The Swedish Interactive Thresholding Algorithm (SITA) uses full threshold and fastpac testing. SITA standard uses a staircase strategy of 4 and 2dB (stimulus increased in 4dB steps until recognized, then decreased below threshold and increased in 2dB steps until just seen), whereas SITA fast uses 3dB steps. The 24-2 and 30-2 programs utilize a 6°

spaced grid offset from the horizontal and vertical meridian, testing 54 and 76 points respectively. Four points are determined initially and these are used as starting levels for neighbouring points. Points are tested twice when the anticipated response is outside 5 decibels of that expected. The SITA program considers many factors when determining which stimulus to present, including age, normative data and patients responses, which are combined and weighted in to the visual field model. The four separate investigative computer applications which interact with each other are:

1. Smart questions which determine the choice of stimulus brightness based on the patients responses.
2. Smart pacing based on the speed of the patients responses.
3. Knowledge of when to terminate the examination - the less reliable locations are tested more.
4. Post-examination process allowing information from individual and neighbouring points to be combined with reliability information for information processing.

The SITA standard test takes half the time of the standard full threshold and the SITA fast takes half the time of the fastpac program with similar accuracy and repeatability (Wild et al., 1999).

The patient should wear a patch over the eye not being tested; preferably keeping both eyes open as keeping one eye shut can be uncomfortable and influence the position of the lid in the eye being tested. The patient should also be corrected for refractive error and for presbyopia to avoid degradation of the light stimulus from optical defocus (Cubbidge, 2006). It has been reported that the averaged macular sensitivity in eyes with dilated pupils (>4mm) decreased 1.26dB per dioptre of blur (Weinreb and Perlman, 1986). The appropriate corrections are provided by Humphrey in the handbook. There is evidence to suggest that perimetric retinal sensitivity is not noticeably influenced over the normal physiological range of pupil sizes, although

active pupillary dilation may produce statistically significant differences (Wood et al., 1988, Kudrna et al., 1995).

4.6.1 Interpretation of visual fields

The visual field is not a stable parameter so differentiating true change (signal) from variability (noise) is not straightforward, as often defects found on an initial test will disappear. In normal subjects the thresholds can vary within a test procedure and from one examination to another by between 2 and 3dB. There is also increased variability in responses to stimuli presented from the central 10 degrees out to 30 degrees eccentricity (Lewis et al., 1986, Heijl et al., 1987). The variability is incrementally higher with eccentricity; higher nasally than temporally and higher superiorly than inferiorly (Heijl et al., 1987). The visual field of a normal individual often fluctuates on repeated testing and this is thought to depend on several factors: fatigue (Hudson et al., 1994); the subject's ability to understand the test; the subject's criteria for deciding whether a light stimulus is present; the clarity of the instructions (Kutzko et al., 2000) and the threshold strategy used. Test duration plays an important role in determining the overall fluctuation as the threshold variability increases when the test is longer. The 'learning effect' has been identified where the patient's baseline visual field test is worse than subsequent tests and is greatest in the superior field and for eccentricities beyond 30° (Wood et al., 1987). It has been shown that in subjects newly diagnosed with glaucoma, those who have had at least one visual field test within the previous several months exhibit minimal learning effects on subsequent visual field testing (Gillespie et al., 2003).

Measures of visual field depression or variability presented on the Humphrey printout include mean deviation (MD), pattern standard deviation (PSD) and glaucoma hemifield test (GHT). The mean deviation reflects the average visual field depression over the whole visual field and is negative when the visual field is depressed compared

with age-specific ‘normal’ values, becoming more negative with increasing depression. The pattern standard deviation reflects focal depression of the visual field and is considered abnormal if the index is outside the normal 5% level. The glaucoma hemifield test assesses whether differences in overall sensitivity between the upper and lower hemifields are compatible with glaucoma. An abnormal visual field is defined as having a GHT ‘outside normal limits’ and/or a PSD worse than $p > 0.05$.

4.6.2 Reliability indices

Fixation monitoring in the Humphrey perimeter is monitored by the test programme periodically presenting the stimulus in the blind spot area (the 7 series perimeters include gaze tracking). Trait anxiety has been shown to affect the stability of gaze fixation (Laretzaki et al., 2011). A patient response in the absence of a stimulus is recorded as a false positive, SITA programmes estimate the rate of false positive catch trials by determining the number of responses that fall outside the normal response time. False negatives are recorded where the patient does not respond to a previously seen stimulus. This may be due to early onset field loss or small scotomas in that area (Bengtsson and Heijl, 2000), although fatigue can be a factor. Fixation losses, false positives and false negatives exceeding 33% are documented as low reliability on the results.

Visual quality has no definitive test; however, different aspects of vision can be assessed using aberrometry, contrast sensitivity, glare testing and perimetry to give an overall representation of visual perception. These parameters have not previously been assessed following LASEK performed with a 213nm solid-state laser.

4.7 Study aim

This was an interventional case series of 10 consecutive patients (19 eyes) requested by the Ministry of Defence. The primary purpose of the study was to determine the minimum amount of time their highly trained personnel needed to be downgraded from

active duty following refractive surgery, with the specific investigation of glare and low contrast vision after laser-assisted subepithelial keratectomy (LASEK). The secondary aim was to determine the effect of LASEK on the visual field.

4.7.1 Sample size

The Ministry of Defence were responsible for recruitment of 20 subjects; however, this number did not come forward for consideration. Yang et al. (2010) had compared total higher order aberrations following LASIK using an excimer laser and based on this data, a sample size calculation using G*Power 3.1 (Faul et al. 2007) using a two-way paired t-test to achieve 80% power at an alpha level of 0.05, indicated a total of 7 participants. It was expected that LASEK performed using a solid-state laser would lead to a smaller increase in higher order aberrations and taking this in to account, a larger sample of 20 subjects was recruited to ensure adequate power.

4.7.2 Subjects

The subjects were recruited by the Ministry of Defence from their elite military forces (Special Air Service (SAS), Special Boat Service (SBS/Marines) and Special Reconnaissance Unit (SRR) over a 9 month period. This was co-ordinated by the Chief Medical Officer based in Hereford. Eighteen male subjects were recruited and assessed (mean age 34.4; SD ± 8.69 years). The Assessments were conducted at Aston University by SM, SS and SAN. The exclusion criteria were: unstable ametropia, one seeing eye, active anterior segment disease, residual or active ocular disease, previous intraocular or corneal surgery, history of herpes keratitis, previously diagnosed autoimmune disease, systemic connective tissue disease or atopy, corneal topographic findings suggestive of keratoconus, pregnancy, use of drugs which may interfere with healing response, inappropriately motivated or do not comprehend the rationale.

Table 4.1 Age, uncorrected vision (UCDVA), prescriptions and corrected visual acuity (CDVA) for subjects included in the study. The left eye of subject 6 marked * was not treated.

Px number	Age	RUDVA	R sphere	R cylinder	R axis	RCDVA	LUDVA	L sphere	L cylinder	L axis	LCDVA
1	33	1.2	-5	-0.5	180	-0.12	1.2	-4.5	-0.5	180	-0.12
2	47	0.8	-3.25	-0.25	70	-0.18	0.6	-3.25	-0.25	50	-0.1
3	40	0.36	-0.25	-1	105	0	0.36	-0.25	-1.25	90	0
4	33	0.7	-1.75	-0.5	45	-0.14	0.7	-2	-0.5	90	-0.14
5	31	0.7	-2.25	-0.5	110	-0.08	0.2	-0.25	-0.75	80	-0.1
6	44	0.36	-1	-0.75	160	-0.1	0.36*	-1.25			-0.1
7	24	0.2	0.75	-1.75	90	0.1	0.3	0.75	-2.25	74	-0.1
8	30	0.14	1.25	-1.75	80	-0.2	0.1	0.75	-1.5	90	-0.2
9	39	0.9	-0.25	-3	97	-0.18	0.9	-0.75	-2.25	86	-0.16
10	21	0.44	-1.25	-0.25	10	-0.2	0.5	-1.25	-0.25	50	-0.18

4.7.3 Experimental procedure

The study followed the tenets of the Declaration of Helsinki and informed consent was obtained by having the subject read, sign and date the Informed Consent Form (prior to any trial related evaluations or procedures). The ethical committee of Aston University, Birmingham approved the study and subjects were free to withdraw at any time without obligation.

Procedures

All patients had a complete preoperative ophthalmic assessment to exclude ocular disease.

1. A detailed history was taken and logMAR uncorrected distance visual acuity (UDVA) was measured at 3m using the ETDRS chart.
2. The logMAR corrected distance visual acuity (CDVA) was measured at 3m using the ETDRS chart using a trial frame at 12mm BVD and loose trial lenses.
3. Contrast Sensitivity testing Contrast sensitivity was measured with the Pelli-Robson letter sensitivity test (Clement Clarke International, Edinburgh Way, Harlow, Essex, UK) (Pelli et al., 1988) using the participant's best refractive correction. The Pelli-Robson chart consists of 16 groups of three uppercase letters that are of constant size but vary in contrast. The groups decrease in contrast by approximately 0.15 log units, ranging from 90% contrast to 0.5% contrast. The test was administered at 1 m under controlled room illumination (approximately 100 cd/ m2). Contrast sensitivity was scored letter by letter to provide more reliable test scores than using the triplet method (Elliott et al., 1991). The scores were recorded as log contrast sensitivity ($\log_{10}$ 1/contrast of letters at the threshold of visibility). When viewed at 1 m, the letters subtend 3°, equivalent to a 20/720 Snellen letter. By using large letters, the contrast sensitivity test is affected minimally by visual resolution factors such as residual

refractive error (Zhang L et al., 1989). The scores have been reported to be repeatable to within ± 0.15 log units (three letters) (Elliott et al., 1990), therefore a change of 0.30 log units (six letters) could be regarded as significant.

4. Glare Sensitivity. Glare sensitivity was measured with the Brightness Acuity Tester (Mentor O & O, Norwell, MA, USA). The Brightness Acuity Tester is an illuminated white hemisphere placed in front of the eye, with an aperture through which a test chart is viewed. The smallest letter seen on the EDTRS chart using the participant's best refractive correction was recorded, then the test was repeated with the glare light turned on to low, medium and high settings in a randomised order.
5. Non-contact tonometry using Reichert 7 (R7) non-contact tonometer (Reichert Inc., Depew, NY, USA), which has been shown to be in close agreement with Goldmann contact tonometry (Jorge et al., 2011). The patient was instructed to lean their forehead on the soft pad in the centre of the forehead rest and fixate on the green target inside the air tube. Three readings were taken from each eye and the average recorded.
6. Visual field testing using the Humphrey Visual Field Analyser (Zeiss Humphrey Systems, San Leandro, CA, USA) with the SITA fast strategy. The patient adapted to the illuminated perimeter bowl for approximately 3 minutes while the procedure was explained. Subjects were tested wearing full refraction plus adequate near correction placed in the lens holder as recommended in the manufacturer’s instruction manual; however, if the cylinder was less than 1.00 dioptre best sphere was used (plus appropriate near correction), to minimise the number of lenses placed in the lens holder which may cause ring scotomas or reflections. The first attempt from the first eye was regarded as a practice run and the test was repeated after a short break.
7. Corneal Scheimpflug imaging (Pentacam, Oculus GmbH). The Pentacam system was used to image the anterior segment of the eye. The patient was

seated with his chin on the chinrest and forehead against the forehead strap and asked to fixate straight ahead on a fixation target. The operator visualized a real-time image of the patient's eye on a computer screen, with the machine marking the pupil edge and centre and the corneal apex, and manually focussed and aligned the image. Arrows displayed on the screen guided the operator's alignment of the instrument in the horizontal, vertical, and anteroposterior axes. To reduce operator-dependent variables, Pentacam's automatic release mode was used.

8. Aberrometry. Aberrometry was performed using Nidek OPD-Scan III with a natural pupil.
9. A cycloplegic refraction using 1% cyclopentolate to paralyse accommodation was compared with the manifest refraction (maximum plus while maintaining best acuity) to allow surgical planning.
10. Slit lamp biomicroscopy with dilated fundus assessment using a 90D Volk lens.
11. Corneal thickness was measured using the Nidek Ultrasonic Pachymeter UP-1000 (Nidek Technologies, Gamagori, Japan). Studies have shown this method to have a high degree of intra-operator, inter-operator, and inter-instrument reproducibility (Miglior et al., 2004, Marsich and Bullimore, 2000). However, this technique requires corneal-probe contact, and so measurement may yield slightly thinner readings as a result of tissue indentation. Alternatively, placement of the probe exactly on the centre of the cornea is operator dependent and crude; consequently off-centre placement may yield thicker measurements than the true central corneal thickness. Mild patient discomfort and risk for infection are additional concerns with a contact technique.

The laser refractive surgery was performed by SS at the Laser and Lens private clinic using the Pulzar Z1 laser system. The procedures were conducted at the Midland Eye Institute in Solihull or the Westbourne Clinic in Edgbaston. A standard LASEK

technique was used (Shah et al., 2001) and bilateral surgery was performed on all but one patient. Mitomycin-C 0.02% was applied for 30 seconds to myopic eyes with an ablation depth greater than 75µm.

Postoperatively, patients received topical ketorolac for 2 days, topical ofloxacin for 1 week and a generic carbomer lubricant as required for up to 3 months. In addition, 3 days of meloxicam 7.5mg were recommended. Patients were examined the next day, then at 1, 2, 4 and 6 weeks post operatively at BBR Optometry Practice in Hereford.

4.7.4 Statistical analysis

Efficacy was evaluated using the mean UDVA (logMAR) at 3 months. The cumulative proportion of eyes falling within each visual acuity group for preoperative CDVA and postoperative UDVA was plotted on a histogram. Safety was assessed on the basis of the change in lines of CDVA between the preoperative visit and the 3-month visit. The safety index was calculated by the formula: mean postoperative CDVA (logMAR)/ mean preoperative CDVA (logMAR). Accuracy was assessed by plotting the attempted change in spherical equivalent (SE) against the achieved change in SE at 3 months, with the linear regression trend line allowing observation of undercorrected and overcorrected eyes. The stability of treatment was evaluated by comparing the mean postoperative SE at 6 weeks and 3 months. Results were displayed using the standard graphs for reporting refractive surgery outcomes (Dupps Jr et al., 2011).

Statistical analysis was performed with SPSS v20.0 (SPSS INC., Chicago, USA). Normally distributed continuous data underwent parametric statistical analysis. Normality was confirmed for the main study data sets using Shapiro-Wilks, $p > 0.05$. Differences between repeated measures were evaluated by dependent t-test or Wilcoxon signed-rank test. A p value of less than 0.05 was considered significant.

4.8 Results

Of the 18 recruits, 6 were unsuitable, 12 underwent laser refractive surgery (mean age 33.3; SD ± 6.9 years). Of the 12 subjects, 12 attended appointments exactly as scheduled the next day, then 10 stayed on schedule for their 1 (mean 7.6 ± 1.8 days), 2 (15 ± 1.65 days), 4 (22 ± 2.4 days) and 6 (47 ± 3.6 days) week appointments post operatively at BBR Optometry Practice in Hereford. Two subjects only attended BBR Optometry Practice the day following surgery, although they attended Aston University at 3 months. A total of 10 attended Aston University for follow-up appointments at three months post-surgery. The age and prescriptions of the 10 participants who returned for follow-up are detailed in Table 4.1. Two participants were lost to follow up due to deployment overseas. The ten remaining subjects attended follow-up appointments on average 14 weeks ± 5 weeks.

The mean central corneal thickness before LASEK measured by Pentacam was 545.6 ± 27.6µm (range 499 to 615µm). The mean central corneal thickness at 3 months following LASEK was 520.7 ± 34.1µm (range 475 to 601µm).

Accuracy

At 3 months, the mean SE was -0.14 ± 0.28D (range +0.25 to -0.75). The linear regression trend line had a gradient of 0.9253 and an intercept value of -0.0031. The R^2 between attempted and achieved SE change was 0.9916. Eleven eyes (58%) were within -0.13 to + 0.13D of the SE, 18 eyes (95%) were within ± 0.50D and 19 eyes (100%) were within ± 1.00D (Figure 1). The mean preoperative astigmatism was -1.04 ± 0.79D (range -0.25 to -3.00D), which was decreased to -0.18 ± 0.19D (range 0 to -0.50D) at 3 months.

Efficacy

At 3 months, the mean UDVA was -0.10 ± 0.08 (range 0.10 to -0.20) logMAR. The UDVA histogram shows the cumulative percentage of eyes within each visual acuity group (figure 1). The efficacy index (ratio of the mean postoperative UDVA to the mean preoperative CDVA) was 0.90.

Safety

The mean preoperative CDVA was -0.11 ± 0.06 (range 0 to -0.20) logMAR and the mean CDVA at 3 months was -0.11 ± 0.06 (range 0.02 to -0.20) logMAR. The change in lines of CDVA is shown in Figure 1. At 3 months the safety index was 1.09.

Stability

The postoperative SE was stable between 6 weeks and 3 months; no eye changed more than 0.50D.

Figure 4.1 Uncorrected Distance Visual Acuity.

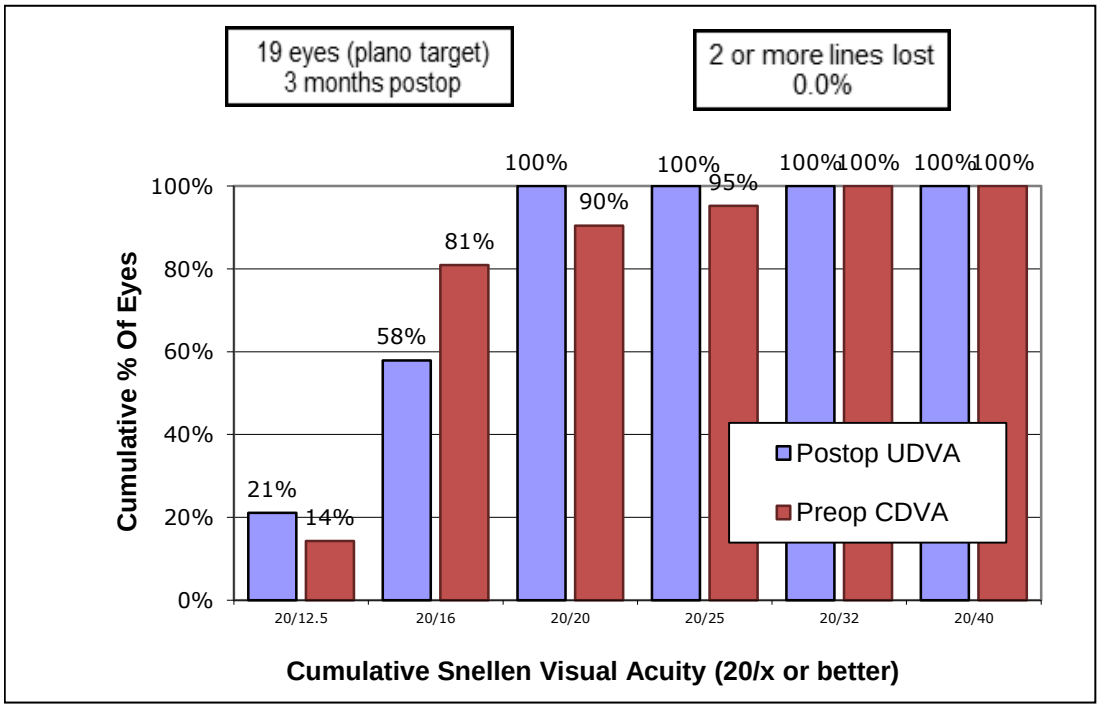


Figure 4.2 Change in corrected distance visual acuity.

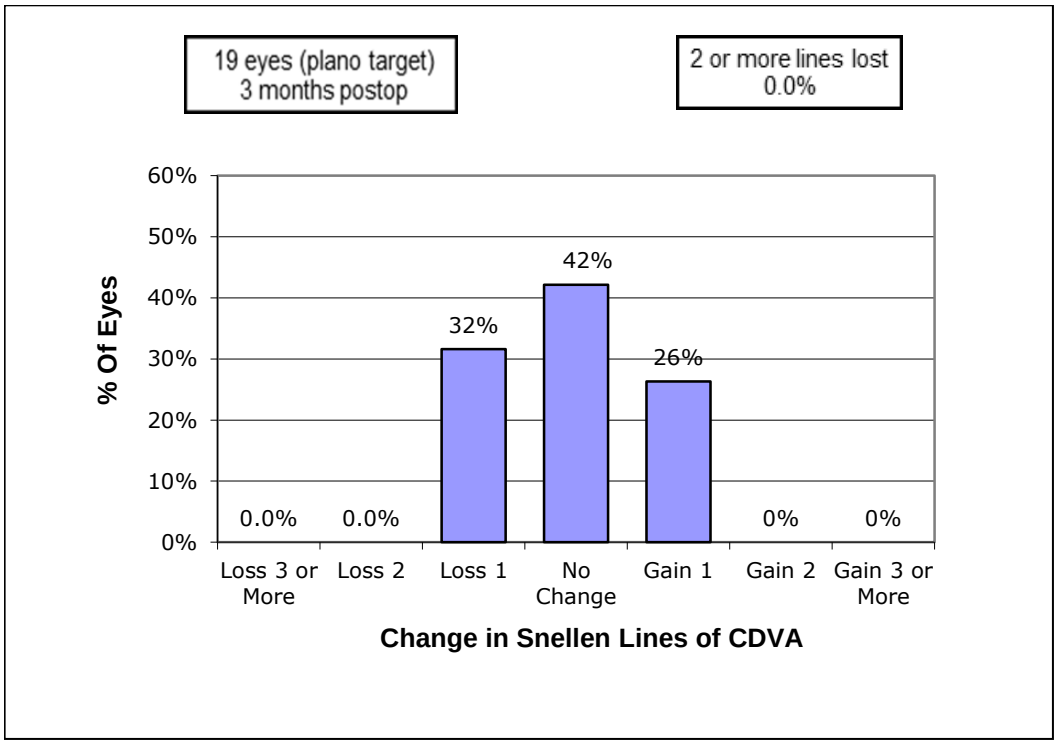


Figure 4.3 The spherical equivalent of attempted versus achieved refraction.

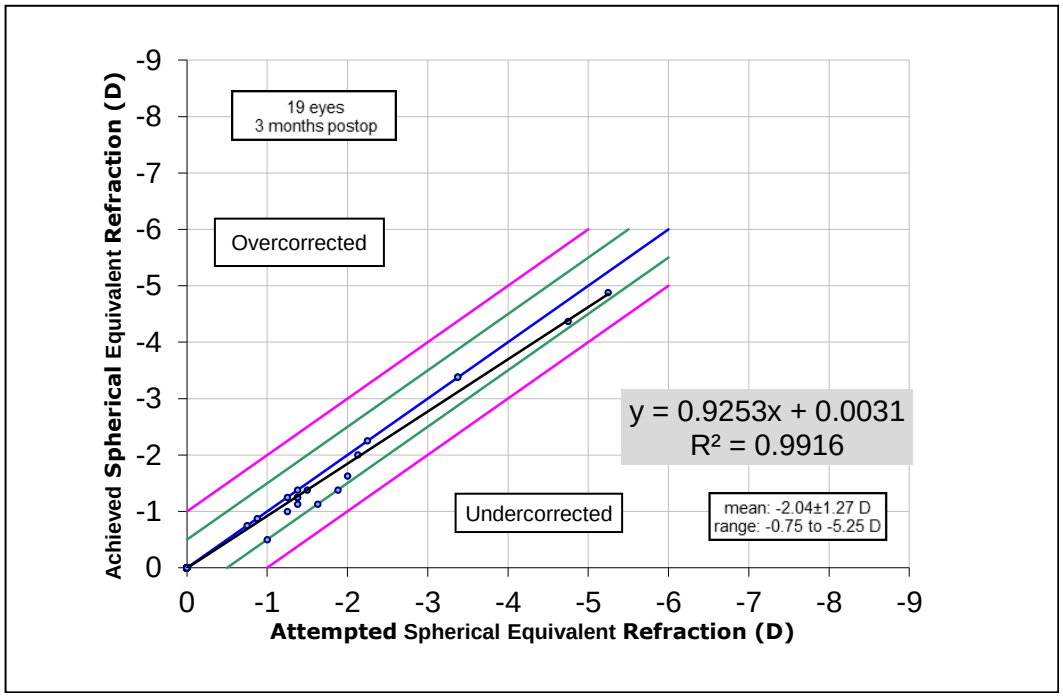


Figure 4.4 The spherical equivalent of refractive accuracy.

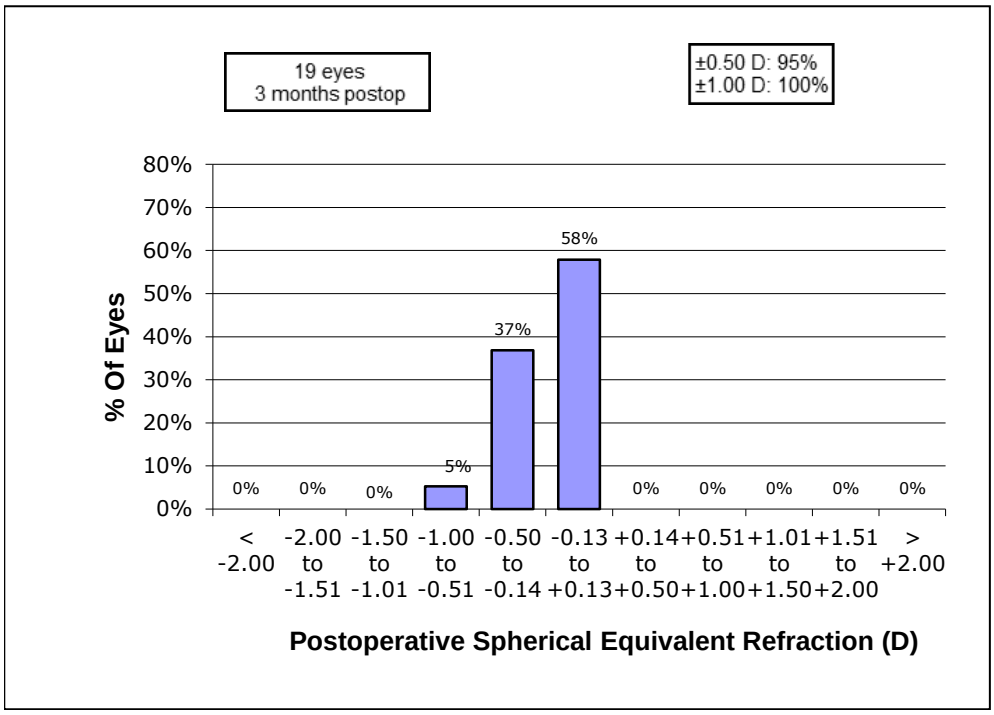


Figure 4.5 Refractive astigmatism.

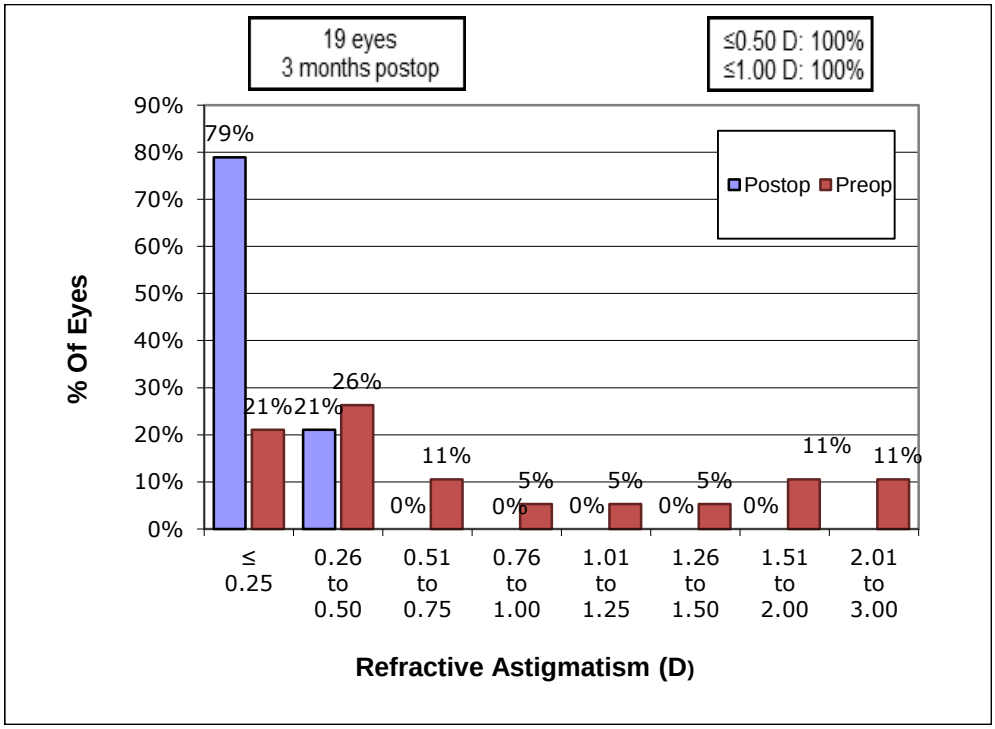
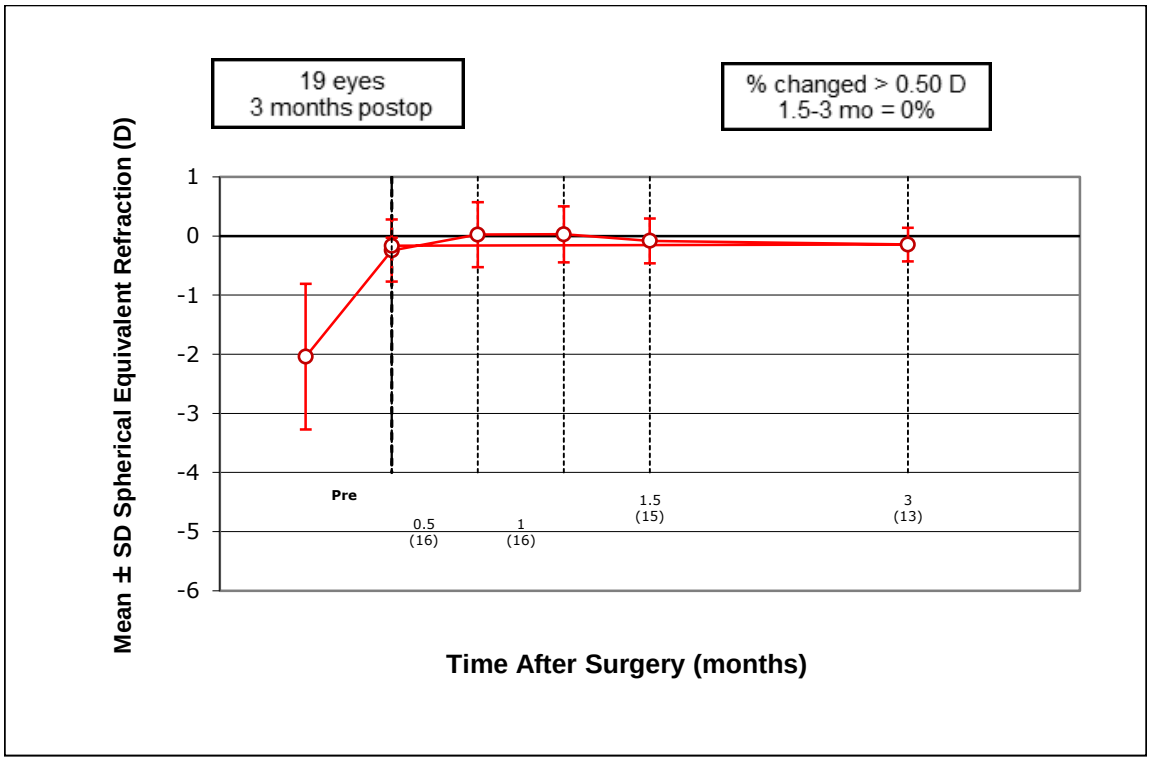


Figure 4.6 Stability of spherical equivalent refraction.



Higher order aberrations

Table 4.2 Preoperative and postoperative HOAs after LASEK with 6mm pupil, analysed by dependent t-test (n = 9).

	Preoperative	**Postoperative at 3/12 postoperative**	**Mean change**	**P value**
Total higher order aberrations (µm)	0.37 ± 0.07	0.60 ± 0.23	0.22 ± 0.23	0.03
Spherical aberrations (µm)	0.07 ± 0.04	0.12 ± 0.10	0.04 ± 0.10	0.22
Coma (µm)	0.16 ± 0.09	0.23 ± 0.17	0.06 ± 0.12	0.17

Contrast sensitivity

The pre-operative contrast sensitivity was 1.92 ± 0.075 logMAR units. At 3 months the contrast sensitivity was 1.93 ± 0.09 logMAR units, p = 0.52.

Table 4.3 Brightness Acuity Test analysed by Wilcoxon signed-rank test (n = 19).

Setting of BAT	**logMAR units preoperative**	**logMAR units 3/12 postoperative**	**P value**
Low	-0.12 ± 0.05	-0.08 ± 0.07	0.08
Medium	-0.12 ± 0.64	-0.09 ± 0.07	0.22
High	-0.11 ± 0.07	-0.08 ± 0.09	0.40

Table 4.4 Summary of results for visual fields data (n = 14).

* Results of dependent t-test comparing preoperative and 3 month postoperative results;

† Results of Wilcoxon signed-rank test

	Preoperative	**3/12 Postoperative**	**P value**
Mean sensitivity (MS)	30.66 ± 0.71	30.98 ± 0.55	0.09*
Mean deviation (MD)	-0.25 ± 0.68	-0.17 ± 0.80	0.61*
Pattern standard deviation (PSD)	1.54 ± 0.35	1.38 ± 0.19	0.19*
False positives (FP)	1.71 ± 2.16	3.71 ± 3.45	0.08†
False negatives (FN)	0.35 ± 1.08	0	0.18 †
Fixation losses (FL)	0.71 ± 0.72	0.78 ± 0.89	0.74 †

4.9 Discussion

The surgeon (SS) recommended LASEK for all individuals in this trial of MOD personnel because they were in active service with demanding roles (the majority of subjects in this study were Marines). Surface ablation procedures are often chosen in preference to LASIK for patients pre-disposed to trauma because there is no stromal corneal flap, therefore avoiding flap complications and LASIK associated keratectasia (Azar et al., 2012). Shorter recovery time and less pain have been reported for LASEK versus PRK (Lee et al., 2001), although LASIK offers the shortest visual recovery and least pain (Azar et al., 2012). There is controversy regarding which technique has the best visual outcome (Kulkarni et al., 2013).

The minimum best corrected vision standards accepted by The Royal Navy Royal Marines is uncorrected: 6/12, N5 each eye and corrected: 6/6, N5 each eye for recruits joining post 1995, although slightly more leniency was allowed prior to this (AOP 2009). Some of the subjects in this study did not reach this standard on entry and had worn contact lenses at their medical; however, others had noticed deterioration in their vision since joining. LASEK permitted all subjects in this trial to reach the minimum visual standards required and no individual had problems with glare which was particularly relevant to night operations.

The accuracy of the refractive outcome was comparable with other studies (Aydin et al., 2008, McAlinden et al., 2011, Shah et al., 2012); no eye lost more than 2 lines of CDVA, two thirds maintained the same CDVA or gained one line postoperatively and 95% of eyes were within ± 0.50D. The only post-operative complication was one case with slight haze, which was treated successfully with steroid drops.

Despite good high contrast vision following refractive laser surgery using an excimer laser; there have been reports of significant correlations between increased higher-order aberrations and decreased contrast sensitivity, especially total higher order

aberrations, coma and spherical aberrations (Yamane et al., 2004, Sharma et al., 2007). Visual symptoms have also been linked with ocular aberrations, such as monocular diplopia with coma, and starburst and glare with spherical aberration (Sharma et al., 2007, Chalita et al., 2003). Results for higher order aberrations in a study evaluating 60 eyes of 34 patients following LASIK using a Pulzar Z1 solid state laser showed a statistically significant increase for total aberrations of 0.2 µm; primary coma 0.17 µm and primary spherical aberration 0.09 µm. The induction of coma was attributed to non-optimised ablation centration (Piñero et al., 2012). In this present study there was an increase in total aberrations for all subjects, with one patient having a three-fold increase. This did not affect his binocular contrast sensitivity, although the monocular values were slightly reduced when compared to his original sensitivity. The rest of the patients achieved the same or slightly better results for contrast sensitivity after LASEK surgery. Values for spherical aberration were reduced in one third of the subjects and only slightly increased for the remainder, and for coma the values for half of the subjects were reduced. When comparing LASEK to LASIK performed with an excimer laser, Kaya et al. reported no change in contrast sensitivity following LASEK, but reduced contrast sensitivity following LASIK at the 6 month time point (Kaya et al., 2004). Kim et al. found an improvement in CS at 3 and 6 cpd post LASEK compared with no change post-LASIK at 6 months. Further improvements at higher frequencies were found following wavefront-guided LASEK (Kim et al., 2007). An interesting finding by Kirwan and O'Keefe was an increase in mean RMS of total HOAs in LASIK and LASEK treatment groups at 3 months postoperatively, with a significantly higher factor increase in the LASIK group. The LASIK group remained stable between 3 and 12 months, however, the LASEK group showed a small but significant reduction in higher order aberrations over the 9 month period (Kirwan and O'Keefe, 2009). A more recent study found CS to be lower in the LASEK group at 3 and 6 months postoperatively, however, this was no longer significant at 12 months (Townley et al., 2012). It is accepted that stromal laser ablation is the primary source of surgically induced higher

order aberrations following LASIK, however, flaps created using a microkeratome increase HOAs (Porter et al., 2003, Pallikaris et al., 2002, Potgieter et al., 2005), whereas the femtosecond laser appears to minimize the disruption of collagen lamellae thought to induce HOAs (Tran et al., 2005). Two studies investigating the inductions of higher order aberrations 3 months after LASIK show post-operatively no correlation between the femtosecond laser flap thickness and the induction of higher-order aberrations, but an association with the level of myopic correction (Cheng et al., 2008, Hood et al., 2013).

There were no significant results for the difference between pre and postoperative brightness acuity testing, although the presence of a glare source did reduce acuity slightly, regardless of the intensity. The incidence of night vision disturbances are of particular significance to soldiers as military operations often take place at night. Straylight (scattered light that does not come to a focus on the retina) can be increased after refractive surgery due to corneal haze, superficial scars or postoperative flap positioning; although this effect has been shown to peak after one month before gradually decreasing (van de Pol et al., 2001). Studies have shown a reduction in straylight after LASIK (Lapid-Gortzak et al., 2010) and LASEK (Lapid-Gortzak et al., 2010, Rozema et al., 2010); however these studies did not use the same method of testing. Of the eyes assessed in this study, those with reduced high contrast post-surgery acuities had similarly reduced acuities under glare conditions. In almost all cases contrast sensitivity was unaffected, which may suggest that the glare experienced in this particular group following LASEK surgery is clinically irrelevant at 3 months.

Detecting and monitoring the visual field is fundamental in glaucoma management, particularly in myopes who are at increased risk of developing the disease (Mitchell et al., 1999). The results for pre- and postoperative automated perimetry showed a small increase in mean sensitivity and decrease in mean deviation indicating an improvement

in performance, although this did not reach significance and may be attributable to the learning effect (Wood et al., 1987). This is similar to the findings of Mostafaei et al. who found no statistically significant differences, but a slight trend in increased sensitivity when they assessed patients 3 months following LASIK on one eye and PRK on the other (Mostafaei et al., 2009). Previous studies assessing LASIK have shown a decreased mean sensitivity in the mid periphery (Brown et al., 2005, Ozdamar et al., 2004, Montés-Micó and Charman, 2002, McCarty et al., 2003), attributed to optical factors rather than changes in perfusion during microkeratome suction causing subsequent damage to the retinal nerve fibre layer. A study with longer follow-up found transient effects returning to normal after 12 months (Lleó-Pérez and Sanchis Gimeno, 2007).

Limiting factors for assessing whether patients recover visual function by 3 months were the small sample size, limited prescription range and the inconsistencies in the time of follow-up. As sample sizes decrease extraneous errors are less likely to be cancelled out and therefore true effects can sometimes be obscured i.e. insufficient power to detect an effect (Cohen 1992). This is particularly true within a sample where there is less is greater variability; in this case the variability in ages, pupil size and to some extend spectacle presciptions would reduce the accuracy of the statistical analysis. The three month time period also meant that this study could only accurately describe short-term outcomes and identify early post-operative complications, although SS pronounced all participants fit to return to active duty at the 3 month time point. This finding was important as there was a high cost to the individuals and their regiments while they were down-graded. There was no control group so a direct comparison of other laser systems or methods was not possible. There was no access to the responses to the post-deployment questionnaire so subjective outcomes could not be evaluated to assess patient satisfaction. All but one patient had bilateral LASEK; therefore, each eye cannot be considered statistically independent. A significant factor

in the 3 month results was fatigue, particularly in 2 participants; one of whom had driven from the north of Scotland with no break and had to return within an hour and a half and the other who had just flown overnight from his deployment.

4.10 Conclusion

LASEK surgery performed with the Pulzar Z1 213nm wavelength solid-state laser appears to be safe and effective; three months would appear to be sufficient time for vision to stabilise enabling the soldiers to return to full duties. Despite an increase in total higher order aberrations, there was no significant decrease in contrast sensitivity or increase in glare disability. Mean sensitivity and reliability indices for perimetry were comparable to pre-surgery results. Modifying the cornea using LASEK with solid-state technology does not appear to have affected the visual field.

4.11 Summary

This chapter showed that refractive laser surgery using LASEK may enhance visual quality; particularly mean sensitivity measured using static perimetry. The following chapter investigates differences between visual field results between myopes who had previously been treated using any technique of refractive surgery more than 2 years ago (and therefore presumed fully healed and stable) and myopes corrected with spectacles.

Chapter 5 – PERIMETRY POST-REFRACTIVE SURGERY

5.1 Introduction

The conflicting results of studies investigating peripheral field loss with LASIK and PRK ((Mostafaei et al., 2009, Brown et al., 2005, Ozdamar et al., 2004, Montés-Micó and Charman, 2002, McCarty et al., 2003), particularly over longer time scales (Lleó-Pérez and Sanchis Gimeno, 2007), warranted further investigation. Ethics were obtained to investigate visual field differences between subjects with vision previously corrected by refractive surgery versus age-matched controls.

5.2 Study aim

The aim of this study was to identify differences between visual field results between myopes who had previously been treated using any technique of refractive surgery more than 2 years ago (and therefore presumed fully healed and stable) and myopes corrected with spectacles.

5.2.1 Sample size

The sample size was calculated based on the information gained from a pilot study of 5 subjects who had previously undergone LASIK (Mean age 29 ± 7.5 years, mean previous Rx -2.30 ± 1.06) versus 5 myopes (Mean age 32 ± 6.7 years, mean Rx -2.75 ± 1.08). The PSD values were compared (1.41 ± 0.23 vs 1.12 ± 0.20) using G*Power 3.1; 2 tailed t-test (mean difference between 2 independent means), for a power of 80% and an alpha level of 0.05. The sample size for each group was 10, so 11 subjects were recruited to allow for drop-out.

5.2.2 Subjects

Subjects were recruited from the Aston University public services clinic and were all staff and students at the university. The exclusion criteria were no previous treatment

for myopia or astigmatism by refractive laser surgery, refractive surgery to correct hypermetropia (due to the difference in profile), contact lens wear, any ocular surface disease, amblyopia, more than 1 year elapsed since their previous eye examination.

5.2.3 Experimental Procedure

The study followed the tenets of the Declaration of Helsinki and informed consent was obtained by having the subject read, sign and date the Informed Consent Form (prior to any trial related evaluations or procedures). The ethical committee of Aston University, Birmingham approved the study and subjects were free to withdraw at any time without obligation.

Visual field testing using the Humphrey Visual Field Analyser (Zeiss Humphrey Systems, San Leandro, CA, USA) with the SITA fast strategy. The patient adapted to the illuminated perimeter bowl for approximately 3 minutes while the procedure was explained. Subjects were tested wearing full refraction plus adequate near correction placed in the lens holder as recommended in the manufacturer's instruction manual; however, if the cylinder was less than 1.00 dioptre best sphere was used (plus appropriate near correction), to minimise the number of lenses placed in the lens holder which may cause ring scotomas or reflections. The first eye was randomised and the subjects had one practice run and a break before their recorded attempt to allow for the learning effect.

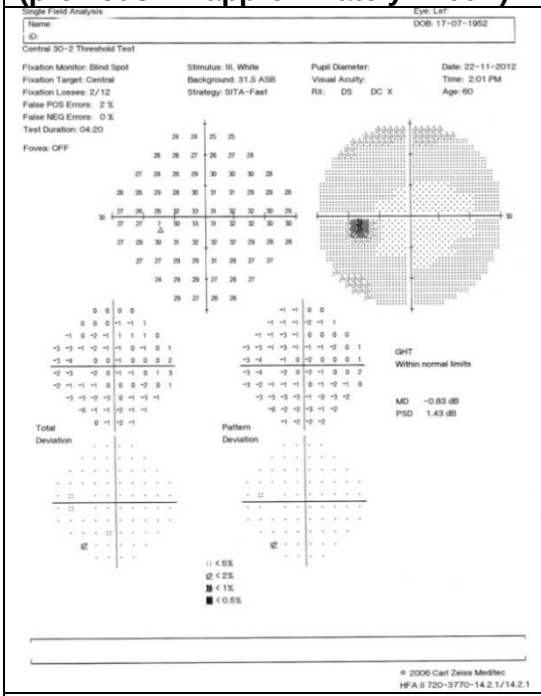
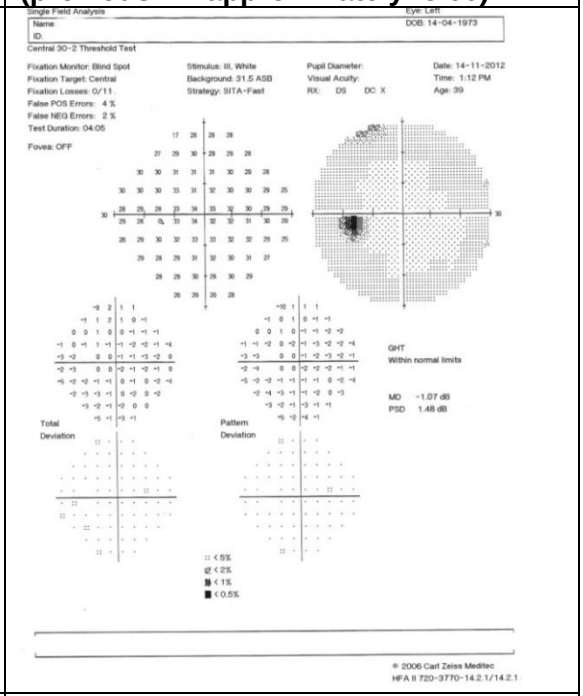
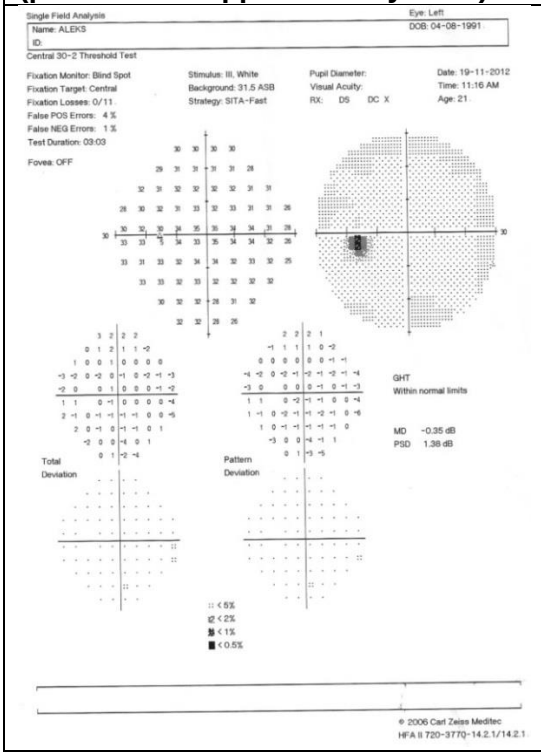
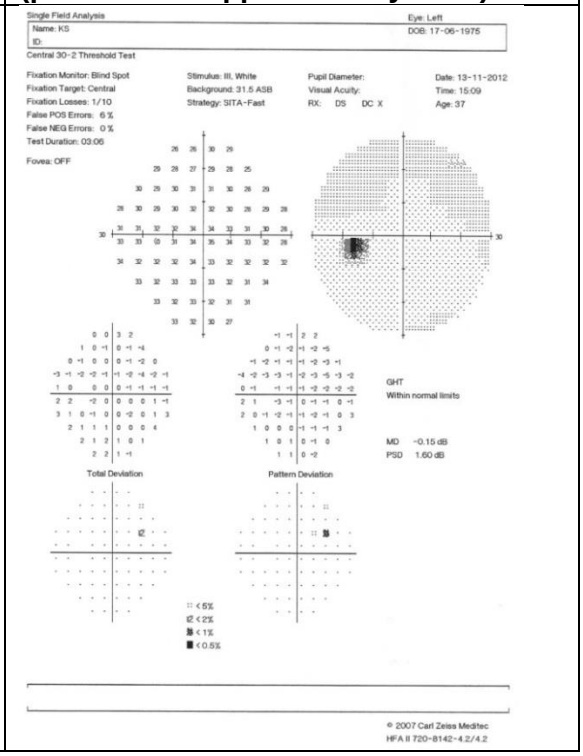
5.2.4 Statistical Analysis

Statistical analysis was performed with SPSS v20.0 (SPSS INC., Chicago, USA). Normality was confirmed for the data sets using Shapiro-Wilks, $p > 0.05$. There were no outliers in the data as assessed by inspection of a box plot. Homogeneity of variances was not violated, as assessed by Levene's Test for Equality of Variances ($p = >0.05$). Differences between measures were assessed by independent samples t-test. A p value less than 0.05 was considered significant

5.3 Results

Twenty two patients took part: eleven subjects who had undergone LASIK between 2 and 20 years ago, mean 5.9 ± 4.8 years ago (Mean age 35.5 ± 11.6 years; Mean Rx: -4.00 ±1.35D) and eleven myopes who had not had refractive surgery (Mean age 36.1 ±12.7 years; Mean Rx: -3.76 ±1.56D). The mean deviations were very similar: MD laser group 1.37 ± 1.07dB; MD non laser group 1.31dB ± 0.17dB, p = 0.64. The PSD was slightly worse in the laser group, although this did not reach significance: PSD laser group -0.37 ± 1.07; PSD non laser group -0.01 ± 0.76, p = 0.14.

Table 5.1 Visual field plots for left eyes of 4 of the additional post refractive surgery subjects. The plots illustrate that although the results are within normal limits, the defects tend to be nasal or temporal, which may reflect the positioning and blending of the optic zone.

Field plot for 20 year post PRK patient (previous Rx approximately -4.00D)	**Field plot for 6 year post LASIK patient (previous Rx approximately -3.00)**
	
Field plot for 1 year post LASIK patient (previous Rx approximately -5.00)	**Field plot for 4 year post LASIK patient (previous Rx approximately -5.00)**
	

5.4 Discussion

The main reason for the choice of a myopic control group was to attempt to control for any differences that could possibly be attributed to myopia. The myopic control group was selected as there had been problems obtaining reliable field plots for all studies and therefore it was important to attempt to control for any effect due to the personality characteristics of subjects selected from a university department.

The variety in age, surgical procedures and time elapsed since surgery limits the usefulness of this data; however, an interesting finding on the field plots for the laser group was a divide of probability symbols, either nasal or temporal of the midline (Table 4.5). This may indicate areas of blending or reflect the symmetry of the blending as these points were generally peripheral. This was not present in the non-laser subjects, however, all the individual field plots were within normal limits and there were no probability symbols greater than $p < 5\%$. The lack of difference between the groups could be due to the majority of subjects from the laser group having had their procedures within 5 years for low to medium levels of myopia and therefore they would most likely have had large optic zones and blended transition zones. It would be interesting to investigate the visual field plots from patients who had their refractive surgery using earlier technology and less sophisticated nomograms or possibly who required higher corrections as there would be more likelihood of seeing a difference, particularly if the optic zone was smaller. Knowledge of the ablation zones used would be helpful to make correlations for the results.

5.5 Conclusion

Mean deviation and pattern standard deviation as determined by perimetry performed using the Humphrey Visual Field Analyser and the SITA 30-2 fast strategy were comparable in myopes corrected using refractive laser surgery more than 2 years previously, compared with myopes who wore spectacles.

5.6 Summary

This chapter showed that refractive surgery performed more than 2 years ago does not appear to have a detrimental effect on the visual field. The following chapter compares the visual quality for two multifocal contact lenses of similar design.

Chapter 6 - PRECILENS C2MULTI VERSUS CIBA VISION AIR OPTIX™ AQUA MULTIFOCAL: A COMPARATIVE STUDY

6.1 Introduction

There is a growing demand for flexible correction following presbyopia, where there is a loss of accommodative function with age. Monovision (where one eye is in focus for distance and the other for near) can reduce stereoacuity, particularly beyond differences of 1.50D and relies on suppression of one eye (Schor et al., 1987). Multifocal contact lenses have near and distance images present at the same time in both eyes, but only one in focus depending on whether the patient is looking at a near or distance object. The out of focus image can, however, lead to ocular rivalry, degradation of the image (Cohen, 1993) and if the patient has incompatible higher order aberrations, a poor visual outcome (Martin and Roorda, 2003).

6.2 Contact lens correction of presbyopia

There are three categories of contact lens corrections open to presbyopic patients who wish to wear contact lenses: supplemental spectacle correction over contact lenses; monovision; and multifocal contact lenses available in soft, gas permeable, hybrid and scleral options. According to a recent international survey (Morgan et al., 2013), 10% of presbyopic contact lens patients are corrected with monovision, however, lower addition patients generally have more success than higher addition patients (Bennett, 2008), particularly as monovision is limited by the inability to incorporate an intermediate prescription without compromising the near or distance refraction (Erickson, 1988). Distance and near acuities measured using high contrast optotypes have been shown to be superior to those achieved with multifocal contact lenses (Gupta et al., 2009), however, stereoacuity is worse due to the disruption of binocularity (Gupta et al., 2009, Richdale et al., 2006).

6.3 Multifocal contact lenses

Approximately 40% of presbyopic patients wear multifocal contact lenses (Morgan et al., 2013). Multifocal contact lenses can be categorised in to ‘simultaneous vision’ or ‘alternating vision’ designs. Simultaneous vision contact lenses have multiple powers positioned in front of the pupil at the same time and the patient suppresses the image that is not in focus for the particular task they are undertaking (Benjamin, 1993). Aspheric, concentric/annular and diffractive lenses use this principle. Alternating vision designs are more common in gas permeable lenses and rely on translation where the lens moves vertically to place the correct zone in front of the pupil. The distance portion is in front of the pupil when the eyes gaze straight ahead and the lids push the lens up on inferior gaze to align the near portion. The use of prism and truncation assist positioning and stability, respectively (Bennett, 2008), however, lid anatomy and blink dynamics can affect success.

6.4 Aspheric contact lens designs.

Asphericity can be applied to anterior, posterior or both surfaces (bi-aspheric) to generate a chosen power. This is accomplished in soft, multifocal designs by the incorporation of controlled spherical aberration; negative in centre-near designs and positive in centre-distance designs. The progressive gradation of power created by the aspheric surface (or surfaces) is rotationally symmetrical and causes a compromise of the image clarity due to the superimposed out-of-focus image; however the advantage is the increased depth of field (Charman and Saunders, 1990). Centre-near designs are most common in soft lenses due to the limited movement associated with this lens type which ensures that the optics are positioned over the visual axis; this is particularly important due to the combined effect of pupil size decreasing with age and pupillary miosis occurring with the near triad (Charman and Saunders, 1990). Pupillary miosis reduces the useful optic of the lens, however, it increases depth of focus and this

combined with neurological aspects of ageing decreases blur sensitivity (Wang and Ciuffreda, 2006). Personality characteristics and anxiety have, however, been linked with a reduced blur tolerance (Woods et al., 2010).

6.5 Methods to assess multifocal contact lens success

The performance of contact lens designs for the correction of presbyopia has been explored from different perspectives. Psychophysical measures of visual quality such as visual acuity and contrast sensitivity, and questionnaires indicating subjective visual satisfaction have been explored in various contact lens designs and wearing modalities. Papas et al. used a rating scale in conjunction with visual acuities (at normal and low contrast levels) and stereopsis to evaluate multifocal contact lens performance. They found a general decrease in performance in the early days of adaption, reflected best by formalised subjective responses (recorded by the numerical rating system) and the range of clear vision at near, rather than acuity based tests (Papas et al., 2009). Gispets et al. evaluated the performance of multifocal contact lenses using visually demanding tasks and found viewing distance and visual demand level significantly affected visual satisfaction. Intermediate viewing or a combination of near and distance viewing were favoured by participants; however, one of the lenses on test was an asymmetrical design and may have acted more like an alternating monovision solution (Gispets et al., 2011).

Objective retinal image quality analysis has been used to show how multifocal contact lenses compromise the quality of vision on an optical basis, indicated by the optical transfer function, axial and off-axis aberrations (Rosén et al., 2012). Pujol et al. used a double-pass technique for distance, intermediate and near with aspheric and spherical multicurve designs at 3 and 5mm pupil sizes. The performance of both lenses was reduced at distance when compared to a single vision lens, however, the multifocals were slightly better at intermediate, and the aspheric multifocal showed the best result

for near vision for small pupil diameters (Pujol et al., 2003). Gifford et al. investigated aberrations induced by centre-near multifocal soft contact lenses and their effect on the contrast sensitivity function (Gifford et al., 2013). Induced primary spherical aberration had previously been shown to create a pseudo-accommodative effect at near (maximum of 2.0D increase in depth of focus with 0.6µm of spherical aberration), however, further increases led to a loss in best corrected visual acuity (Rocha et al., 2009). The findings of a negative shift in primary spherical aberration and positive shift in secondary spherical aberration was equivalent to a -0.50D shift affecting near vision, with an associated reduction of the contrast sensitivity function. The conclusion was that distance back vertex power needed to be corrected accurately if the near vision benefits of induced spherical aberrations were to be exploited effectively (Gifford et al., 2013). Bakaraju et al. used a single-pass method (model eye) to evaluate the performance of 8 multifocal contact lenses with high- and low-add powers and a single vision control at 3 different pupil sizes. Performance was dependent on the add power, design, pupil size and centration: low additions performed consistently better than high additions at all pupil sizes; increased pupil size (>3mm) correlated with decreased performance and decentration was not necessarily detrimental. Results for model eyes have limitations, however, as chromatic aberrations and psychophysical effects play a significant role in visual perception (Bakaraju et al., 2012). Plainis et al. evaluated the effect of pupil size and spherical aberration with three aspheric centre-near multifocal contact lenses in cyclopleged pre-presbyopic subjects. They found that the patient's distance vision was always better with a 6mm rather than 3mm pupil, however, improvement in through-focus visual acuity and depth of field was best for small pupils and binocular vision. Patients with inherent negative spherical aberration achieved better near vision with the centre-near profiles and improved binocular versus monocular performance was attributed to binocular summation (Plainis et al., 2013).

In summary, the main reason for multifocal contact lens discontinuation as reported in the literature is insufficient quality of vision. Small pupils (3mm) give better near acuity with centre-near designs and binocular summation is a key factor in interpreting the slightly out-of-focus images produced (Plainis et al., 2011). The compatibility between the patient's inherent aberrations and the lens design would appear to be an important indicator of success; however, patient's subjective responses give a more effective representation of how well the lenses perform than traditional acuity metrics.

6.6 Study aim

This was a prospective, cross-over and single-masked trial. The primary objective of the study was to evaluate the subjective visual performance including the perception of visual degradation for C2 Multifocal (C2M) in comparison to Air Optix™ Aqua Multifocal (AOAM). The secondary objective was to evaluate the comfort at different stages of wearing. Aston University was one of six international sites evaluating the new lens. The study was co-ordinated by the JENVIS Research Institute at the University of Applied Sciences in Jena, Germany.

6.6.1 Sample size

The sample size was 60 in total; 10 per site as specified by the JENVIS Research Institute. The power for the entire study (multi-centre crossover trial) was calculated by Jenvis Research to be 80% at a significance level of 0.05, as specified in the study protocol.

6.6.2 Subjects

A total of 10 subjects participated in the study. The study was conducted at Aston University and the subjects were recruited by the same investigator (SM) from the

optometry public service clinics. Nine of the participants habitually wore single vision contact lenses and an additional spectacle prescription for reading as required (Table 5.1). The exclusion criteria were: aged <40 years, unable to handle contact lenses and lens care products, 0.30 logMAR or worse distance VA in each eye, ametropia greater in sphere than -6.50 D or +5.50 D with astigmatism of >-0.75D (corneal vertex =14mm), unwilling to use the habitual lens care product for trial period, requiring concurrent ocular medication, eye injury or surgery within twelve weeks immediately prior to enrolment for this trial, pre-existing ocular irritation that would preclude contact lens fitting, currently enrolled in an ophthalmic clinical trial, evidence of systemic or ocular abnormality, infection or disease likely to affect successful wear of contact lenses or use of their accessory solutions, known sensitivity to any of the study solutions, is pregnant or nursing, irregular astigmatism or monovision.

Table 6.1 Prescriptions, eye dominance and habitual contact lenses for subjects included in the trial.

Subject	Rx RE (D)			Rx LE (D)			Add	Dominant eye	Habitual lenses	Manufacturer
	Sphere	Cylinder	Axis	Sphere	Cylinder	Axis				
1	+1.75	-0.75	100	+1.25	-0.50	80	+2.00	R	Air Optix Aqua	Ciba Vision
2	-0.75	-0.25	180	-0.75	-0.50	180	+1.75	R	Aqua comfort plus	Ciba Vision
3	-3.00	-0.50	175	-3.25	-0.75	25	+2.00	R	Acuvue bifocal	Johnson and Johnson
4	-6.50			-6.50			+1.00	L	Easyvision Irasian Sphere	Ciba Vision
5	-2.50	-0.75	180	-2.75	-0.25	5	+2.25	R	Purevision	Bausch and Lomb
6	+1.50			+1.50			+2.00	R	Purevision	Bausch and Lomb
7	+2.00			+2.00			+1.75	L	Acuvue Oasys	Johnson and Johnson
8	+3.00			+3.00			+2.00	R	Air Optix Aqua	Ciba Vision
9	-1.00	-0.50	100	-1.00	-0.50	70	+2.00	R	Acuvue Oasys	Johnson and Johnson
10	-3.00			-3.00			+1.50	R	Air Optix Aqua	Ciba Vision

6.6.3 Experimental procedure

Trial contact lenses and materials

The subjects used their habitual contact lens solution and the contact lenses detailed in Table 5.2. Fitting protocol was carried out following the manufacturer's fitting guidelines. Ocular dominance was assessed as an aid to fitting. The patient wore their distance correction while a +0.75 lens was alternately placed in front of each eye independently under binocular conditions. The patient was asked to report when they experienced the greater visual disturbance in the distance to determine the dominant eye. The end-point for fitting was when the patient decided the best compromise in distance, intermediate and near vision had been reached and over-refraction offered no improvement. A high addition was used in all but one participant, who preferred the low addition option in both lenses. One participant was fitted with a high and medium addition combination for AOMF, although high additions were used in the C2M.

Table 5.2 Details of the contact lenses used in the trial.

	Test product	**Control product**
Name	C2MULTI	AIR OPTIX™ AQUA MULTIFOCAL
Description	Progressive SCL	Progressive SCL
Design	Aspheric	Aspheric
Material	Filcon II 3	Lotrafilcon B
Coating	None	Plasma coated
Water content	58%	33%
Base curve	8.60	8.60
Diameter	14.20	14.20
Spherical Rx available for trial	-6.00 to +6.00D in 0.25D steps	-6.00 to +6.00D in 0.25D steps
Add available for trial	LOW and HI	LOW; MED and HI
Storage solution	Borate buffered saline solution	Isotonic phosphate buffered saline
Labelling	Commercial foil on blister	Commercial foil on blister

Procedure and data collection

The study followed the tenets of the Declaration of Helsinki and informed consent was obtained by having the subject read, sign and date the Informed Consent Form (prior to any trial related evaluations or procedures). The ethical committee of Aston University, Birmingham approved the study and subjects were free to withdraw at any time without obligation. The demographic information such as subject's gender and age was

collected and the subject's visual acuity (VA) measured following refraction using loose lenses and a trial frame at 12mm BVD. The best corrected visual acuity was recorded using an EDTRS chart for distance (recorded in logMAR) and a decimal reading chart (Appendix 2) supplied by the JENVIS Research Institute for near. The near values were converted to logMAR for ease of comparison with other studies (Holladay, 1997). A slit lamp biomicroscopy evaluation, including the use of sodium fluorescein dye was performed to assure that the subject had no signs of any acute ocular infections, injuries, or other abnormalities that would prohibit participation or warrant discontinuation from the trial. Biomicroscopy was also performed during each follow up visit. Keratometry measurements were taken at baseline and lens fit variables and lens performance variables (e.g. wettability and deposits, subjective vision) were assessed by the investigator (SM). The subjects rated subjective comfort and reported symptoms and problems if there were any. At the end of the trial the refraction was compared with baseline and keratometry was repeated if the VA was decreased by 2 log steps or more in comparison to baseline.

The schedule of visits is summarised below:

The appointments were made at a visit for the next visit.
If a subject missed a visit, they were contacted immediately.

Visit 1 = Baseline Visit/ Dispensing Visit:

Agreement for wearer participation in the study (Informed Consent)
Initial visit - Refraction and visual requirements evaluation (Screening Form)
Biomicroscopy (Slit Lamp Findings Form)
Evaluation of current lenses (Symptoms Form)
Dispensing of first trial lenses and assessment of lens fit (Dispensing Form)
Test period (14 days ± 3 days after Visit 1)

Visit 2=Cross-over Visit:

Evaluation of first trial lenses (Subject Questionnaire + Lens Assessment Form)

Biomicroscopy (Slit Lamp Findings Form)

Dispensing of the second type trial lenses and assessment of lens fit (Dispensing Form)

Test period (14 days ± 3 days after Visit 2)

Visit 3=Trial Exit Visit:

Evaluation of second trial lenses and preference check (Subject Questionnaire; Final Questionnaire + Lens Assessment Form)

Biomicroscopy (Slit Lamp Findings Form)

Trial completion (Trial Exit Form)

Adverse event or protocol deviation

The criteria to stop the study for a subject were:

- any change in the wearer's condition making them corresponding to an exclusion criterion
- any lack of tolerance to the contact lenses tested
- the wish of the wearer to stop the study
- to guarantee the wearer's safety or well-being

The other cases of protocol deviation (abandonment of the study, contact lenses not worn…) as well as unexpected change of ophthalmic lenses were documented.

5.6.4 Randomisation

The subjects were randomly divided into 2 groups assigned to wear either C2M or AOMF first for 2 weeks and then the other multifocal soft contact lens for the next 2 weeks.

5.6.5 Statistical analysis

Statistical analysis was performed with SPSS v20.0 (SPSS INC., Chicago, USA). Friedman's ANOVA was used on the ordinal data; the Chi-Square (χ^2) value, degrees of freedom and associated significance were reported. Follow-up paired comparisons were performed with the Wilcoxon signed-rank test; the z-score and associated significance were reported. The Shapiro-Wilk test was used to assess normality of the interval data and where the significance value was less than 0.05, data analysis was conducted using Friedman's ANOVA. The Wilcoxon signed-rank test was conducted for follow-up paired comparisons. Effect size was calculated using Pearson's correlation coefficient. Where the significance level testing using the Shapiro-Wilk was greater than 0.05, paired sample t-tests were applied. A p value of less than 0.5 was considered significant.

5.7 Results

Three male and seven female subjects aged between 49-58 years, mean ± SD: 54.4 ± 3.2 years participated in the trial. Two subjects reported difficulties with the Precilens C2 Multi and did not complete the trial. The first subject to finish the trial early reported difficulties with 'folding lenses which would not stay in'; this participant had already successfully tried the Air Optix™ Aqua Multifocal lens. The second subject tried the Precilens C2M only and concluded their participation in the trial citing unacceptable visual quality. Five participants reported insertion difficulties with the Precilens C2Multi reporting that it was 'a stiff, dry lens which seemed to blink out easily,' particularly immediately after insertion. One subject lost a Precilens C2 Multi lens on the first day of the trial when he 'blinked it out' and had to be given a replacement.

The mean number of trial lenses used in fitting was 1.9 ± 0.7 for the Air Optix™ Aqua Multifocal lens and 1.8 ± 0.4 for the Precilens C2 Multi.

Table 5.3 Results for Friedman's ANOVA showing mean and standard deviations comparing questionnaire responses from subjects following two weeks wearing Air Optix™ Aqua Multifocal versus two weeks wearing Precilens C2 Multi.

Question	**AOMF**	**C2M**	χ^2 **(2)**	**p**
Overall lens satisfaction	7.00 ± 1.41	5.00 ± 2.49	5.813	0.055
Initial comfort	8.67 ± 1.63	8.00 ± 2.16	4.345	0.114
Comfort during the day	9.00 ± 1.24	7.44 ± 2.21	8.083	0.018
Comfort at the end of the day	8.67 ± 1.82	6.88 ± 3.01	2.381	0.304
Overall comfort	8.67 ± 1.63	7.00 ± 2.62	3.692	0.158
Dryness throughout the day	8.56 ± 1.49	7.67 ± 2.94	0.960	0.619
Dryness at the end of the day	7.76 ± 1.94	7.25 ± 2.68	0.261	0.878
Quality of far vision during the day	7.78 ± 1.39	7.33 ± 2.00	5.688	0.058
Quality of intermediate vision during the day	7.76 ±1.41	6.89 ± 2.18	0.467	0.792
Quality of near vision during the day	6.89 ± 1.59	4.89 ± 2.13	5.886	0.053
Consistency of vision throughout the day	9.44 ± 0.95	8.11 ± 2.33	1.615	0.446
Overall vision quality during the day	7.78 ± 1.13	6.22 ± 1.68	6.067	0.048
Quality of far vision at night	8.00 ± 1.41	6.75 ± 1.85	7.440	0.024
Quality of intermediate vision at night	8.11 ± 1.52	6.25 ± 2.22	6.000	0.050
Quality of near vision at night	7.00 ± 1.56	4.25 ± 1.78	9.852	0.007
Consistency of vision at night	8.56 ± 1.16	7.50 ± 2.00	1.231	0.540
Overall vision quality at night	7.44 ± 1.49	6.00 ± 1.50	4.560	0.102

Table 5.4 Results for Slit lamp findings showing mean and standard deviations for subjects following two weeks wearing Air Optix™ Aqua Multifocal versus two weeks wearing Precilens C2 Multi.

Slit lamp findings after lens removal	**AOMF**	**C2M**	**z**	**P**
Limbal redness	2.30 ± 1.41	2.00 ± 1.82	-0.966	0.33
Bulbar redness	3.44 ± 0.83	3.56 ± 1.65	-0.272	0.79
Epithelial staining	0.33 ± 0.66	1.11 ± 1.28	-1.890	0.06
Conjunctival staining	1.00 ± 0.94	1.67 ± 1.33	-1.318	0.19

Table 5.5 Results showing mean and standard deviations for Lens Surface characteristics of Air Optix™ Aqua Multifocal versus Precilens C2 Multi following two weeks wear.

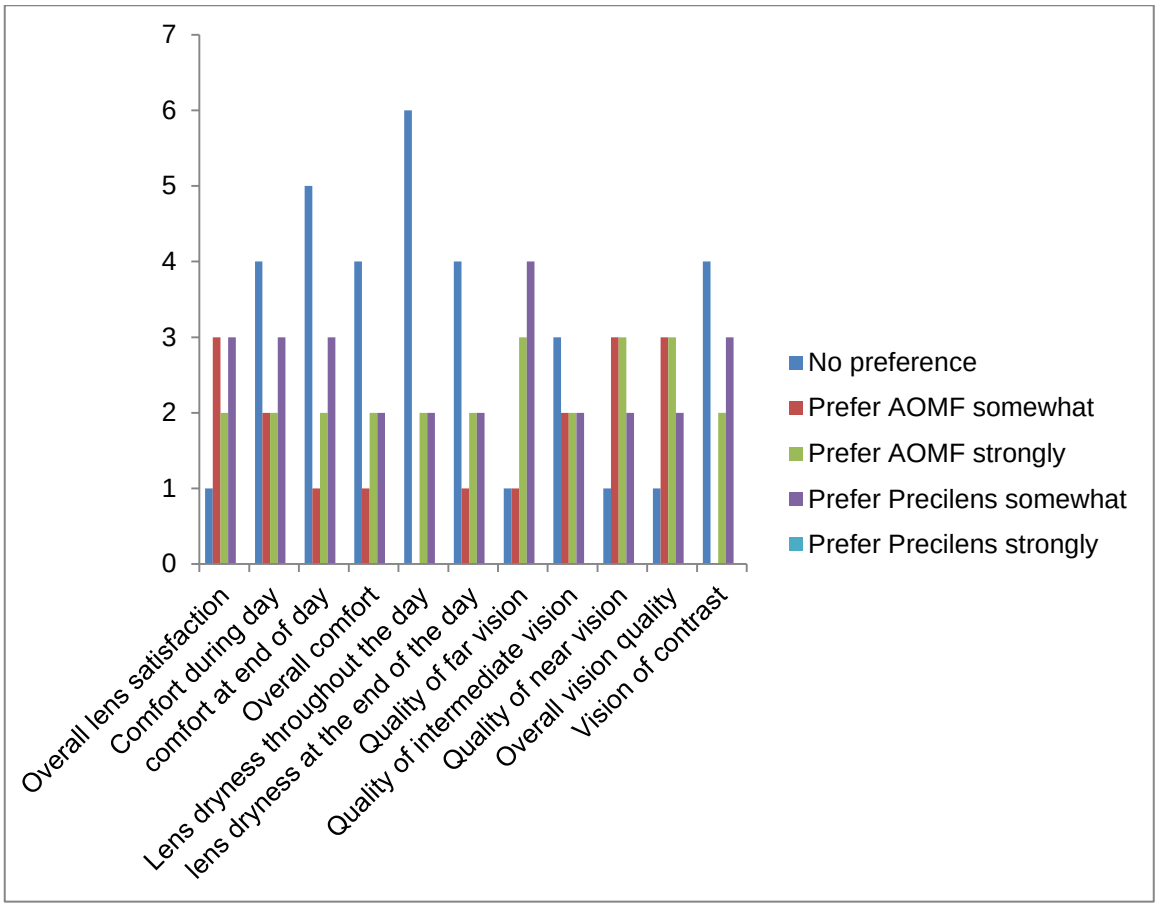
Lens surface characteristics	AOMF	C2M	z	p
Front surface deposits	0.22 ± 0.62	0.13 ± 0.33	-1	0.32
Dry areas/non-wetting	0.00 ± 00	0.25 ± 0.66	-1	0.32
Haziness/filmy/oily	1.56 ± 1.77	1.00 ± 2.00	-0.552	0.58

For significant results, follow-up comparisons were conducted using the Wilcoxon signed-rank test. For comfort during the day, pairwise comparisons yielded a significant result for subjects preferring their own lens over Precilens (Z = -2.23, p = 0.03, r = -0.74). Pairwise comparison for 'Overall vision quality during the day' yielded a significant result for subjects preferring AOMF over Precilens (Z = -2.2, p = 0.03, r = -0.733). For 'Quality of far vision at night', pairwise comparisons yielded a significant result for subjects preferring their own lens over Precilens (Z = -2.226, p = 0.03 r = -0.742) and for subjects preferring AOMF over Precilens (Z = -1.219, p = 0.22, r = -0.406). For 'Quality of near vision at night', pairwise comparison yielded a significant result for subjects preferring AOMF over Precilens (Z= -2.207, p = 0.03, r = -0.735) and for subjects preferring AOMF over own lens (Z = -2.371, p = 0.02, r = -0.790). Regarding 'Final v/a distance', pairwise comparisons yielded a significant result for subjects preferring AOMF over own lens (Z = -2.371, p = 0.02, r=-0.790) and also over Precilens (z = -2.207, p = 0.03, r = -0.735)

Table 5.6: Results for paired t-test comparing mean final binocular visual acuities in logMAR of Air Optix™ Aqua Multifocal versus Precilens C2 Multi, BDVA: binocular distance visual acuity, BNVA: binocular near visual acuity.

	AOMF	C2M	P value
BDVA	0.00±0.09	0.04±0.09	0.06
BNVA	0.14±0.08	0.23±0.13	0.06

Figure 5.1: Graph showing final lens preferences for Air Optix™ Aqua Multifocal (AOMF) versus two weeks wearing Precilens C2 Multi (n = 8).



5.8 Discussion

This study aimed to assess the visual performance and comfort of the C2 Multifocal (C2M) in comparison to Air Optix™ Aqua Multifocal (AOAM). The lenses were similar in design in that they were both hydrogel, aspheric, centre-near, multifocal soft contact lenses. The main physical differences were the higher water content and the lack of plasma coating of the test lens. This was to ensure a fair comparison as different designs favour different tasks (Bennett 2008). Subjects perceived overall visual quality, final distance visual acuity and quality of far and near vision at night to be superior with AOMF, however, overall lens satisfaction was similar.

The recruitment of more female than male participants reflected the higher proportion of female contact lens wearers in the general population, widely attributed to cosmesis (Morgan et al., 2011). International contact lens prescribing for presbyopia has been estimated at 40%, with three times more multifocal soft contact lenses being fitted than monovision (Morgan et al., 2013). Clinician's fitting skills, perceived risk of patient's loss of confidence in the practitioner and the absence of a lens without visual compromise have been cited as reasons for the low rate of fitting (Morgan et al., 2011).

Ocular dominance was assessed as an aid to fitting; however, research has shown that ocular dominance can change with different test conditions, the level of attention and at different positions in the visual field (Ooi and He, 1999). The lens centration, movement on blinking and the pupil size have an effect on the performance of multifocal contact lenses (Charman and Saunders, 1990). The pupil size was not measured in this study and so the contribution of this factor was unknown. The lenses centred well or in a few cases were acceptably tight, so the influence of a loose fitting lens with excessive movement on blinking could not be ascertained from this sample.

Simultaneous vision relies on the brain's natural ability to choose between the two (near and far) images produced by the different optical elements of the contact lens,

depending on what the wearer is looking at. When a distant object is viewed, a sharp retinal image is provided by those parts of the lens within the pupillary area that have distance correction and a somewhat blurred image is provided by the other parts of the lens. These images are superimposed on the retina. The roles of the corrections change when a near object is observed; then, those regions of the lens occupied by the near correction provide the correctly focussed retinal image. This involves a compromise in which the depth of focus for high contrast targets is gained at the expense of contrast sensitivity, particularly in lower light levels or when the target contrast is low (Plakitsi and Charman, 1995).

Current lens wearers motivated not to wear spectacles have been identified as the most likely successful candidates with multifocal lenses (Bennett, 2008) and all participants in the study were keen to try a multifocal lens. The number of trial lenses used for fitting was similar for each type of lens; the slightly higher figure for AOMF was probably due to the availability of a medium power, whereas there were only high and low addition options for C2M.

When comparing the final visual acuities, there was no significant difference for distance or near, despite the questionnaire results showing a significant result for subjects preferring the distance vision with AOMF in preference to their own lens and Precilens C2M. Values for similar comparative studies using AOMF were not available in the literature, however, Gupta et al. (2009) obtained VA values of 0.08 ± 0.10 and 0.27 ± 0.09 logMAR with the high addition Bausch and Lomb Pure Vision aspheric simultaneous vision multifocal lens (Bausch and Lomb, Rochester, NY, USA) for distance and near vision, respectively. This study included patients with a wider age range (49 to 67 years), and allowing a maximum spectacle astigmatism level of 1.00D, whereas it was just 0.75D in the present study. In our study there was also one subject with low near additions in both lens types and one with a medium and high combination in AOMF, however, they both had good near acuities. Therefore, methodological

differences as well as different lens designs could also account for the differences to some extent. A study found stereoacuity and visual acuity to be better with Cibavision Focus Progressive (Ciba vision, Southampton, Hants, UK) versus Bausch and Lomb PureVision Multifocal contact lenses, obtaining VA values of 0.02 ± 0.08 and 0.06 ± 0.06 logMAR for distance and near vision, respectively. Differences in asphericity were cited as one possible reason for the difference in performance (Ferrer-Blasco and Madrid-Costa, 2010). A study compared visual performance through spectacles and a multifocal contact lens under induced glare using the Vistech Functional Vision Analyzer (Stereo Optical Co, Inc, Chicago, IL, USA) and found logMAR values of -0.01 ± 0.03 for binocular distance visual acuity and -0.02 ± 0.05 for binocular near visual acuity for subjects wearing the high addition Bausch and Lomb Pure Vision multifocal contact lens under photopic conditions. The performance for contrast sensitivity was found to be better through spectacles (Llorente-Guillemot et al., 2012). This group (Madrid-Costa et al., 2013) went on to compare the PureVision Multifocal Low Add and the Acuvue Oasys (Johnson and Johnson Visioncare Inc, Jacksonville, Florida, USA) for Presbyopia medium add, which has an anterior zonal refractive aspheric surface and a posterior aspheric design. The use of lower addition lenses in this study was due to the younger cohort aged 45.1 ± 2.3 years. The results for distance were 0.01 ± 0.08 for the Acuvue and 0.00 ± 0.08 for the Purevision, with near acuities of 0.20 ± 0.05 and 0.15 ± 0.08 respectively. The group of 20 subjects had a maximum cylindrical correction of 0.50, a mean spherical refraction of +0.35 ± 1.78D (from +2.25 to -2.50D) and a mean near spectacle addition of +1.48 ± 0.18D (range +1.25 to +1.75D). Again the distance acuities were not too dissimilar to other studies, including this present study, however, the near results of the Acuvue lens were more similar to those we achieved with the Precilens C2M and Gupta (Gupta et al., 2009) with the Pure Vision lens.

This present study had the smallest cohort of all those compared as it was intended to be part of a larger study, however, the fact that other studies have similar results illustrates that good distance high contrast visual acuities can be achieved with multifocal lenses. The results for the questionnaire revealed the quality of the distance vision to be worse at night than during the day when compared to the subject's own single vision lenses. The study by Madrid-Costa et al. (Madrid-Costa et al., 2013) comparing Acuvue Oasys multifocal contact lenses (anterior multi-zonal refractive surface) with Purevision multifocal contact lenses (continuous power gradient design) showed a reduced performance for the Acuvue Oasys multifocal contact lens, which led to the suggestion that in larger pupil diameters, multifocal designs based on a continuous power gradient could provide better visual quality than multi-zonal refractive designs. However, the findings from this current study suggest that differences in performance can be found in similar designs, so other factors may be also be important e.g. whether the power gradient is gradual or rapid, which may interact with individual aberration profiles (Plakitsi and Charman, 1995, Efron et al., 2008) and therefore show more effect in increased pupil sizes, where higher order aberrations are increased. The subjects reporting the worst near acuities in this present study also had poor tear quality, which may have been further exacerbated by contact lens wear causing reduced stability of the prelens tear film (Efron et al., 2008).

Limitations for this study were primarily the potential bias introduced towards AOMF lenses as there were three subjects who routinely wore these lenses, although this was not specified as an exclusion criterion. The high visual demands of this particular cohort of subjects may also have affected patient satisfaction, although tear quality was an issue for some. In practice, patients often accept the visual compromise of a multi-focal contact lens and are happy to wear them in social situations, where their near acuity is less critical. All the subjects reported difficulty with eyestrain when trying to complete their normal work tasks, which involved a large amount of near and

intermediate work. These results may suggest that the lenses studied provide an acceptable distance visual quality, but an insufficient near add choice. Therefore, the practitioner should consider individual's needs and demands for near and distance vision, when deciding which type and power of multifocal contact lens corrections should be fitted.

5.9 Conclusion

The study described in this chapter showed that multifocal lenses provide a reasonable overall quality of vision during the day and that of the two lenses, Air Optix™ Aqua Multifocal (AOMF) was perceived to be superior by the subjects. Despite this, the comparison for overall lens satisfaction did not quite reach statistical significance, indicating that other factors are important in determining patient’s satisfaction with a lens. A key finding was the reduced near acuity in some subjects, most marked in those with poor tear quality, which possibly caused an irregular optical surface creating additional higher order aberrations.

5.10 Summary

This chapter demonstrated that different designs of aspheric multifocal contact lenses do not offer the same performance and that poor tear quality can have an impact on the visual quality in all multifocal contact lenses. The following chapter develops the concept that multifocal lenses may cause visual degradation by assessing perimetric sensitivity and photographic image quality.

Chapter 7 - THE EFFECT OF MULTIFOCAL CONTACT LENSES ON VISUAL FIELDS AND FUNDUS PHOTOGRAPHS

7.1 Introduction

In Chapter 5, the effects of visual degradation were compared for two aspheric designs of multifocal contact lenses. In this chapter the effects of an aspheric multifocal contact lens will be compared with an aspheric single vision contact lens for standard automated perimetry and photographic image quality.

Age is a risk factor for many eye diseases (de Jong, 2013) and assessment for several conditions involves imaging and visual field assessment. Multifocal contact lenses and multifocal intraocular lenses rely on the same optical principals (diffractive or refractive) to simultaneously correct distance and near vision. New technology and improved optics have increased the demand for multifocal correction and it is important to understand the implications of this regarding visual screening and monitoring. The division of available light to provide multiple foci by multifocal contact lenses in the phakic patient and multifocal intraocular lens implantation following cataract surgery may result in a significant compromise of image quality for the clinician observing through the lenses, making screening, monitoring and treating ocular disease difficult. Higher order aberrations are especially deleterious in attempts to image the retina at very high resolution (Miller et al., 1996). Studies have shown that a grating target viewed through various multifocal intraocular lenses was blurred (Inoue et al., 2011) and artefacts have been reported on OCT images through a diffractive multifocal intraocular lens (Inoue et al., 2009).

Standard automated perimetry (SAP) is the most commonly used method to assess the visual field and the SITA testing protocol for glaucoma evaluation has shown excellent sensitivity and reliability (Sekhar et al., 2000). The SITA fast test is an even shorter threshold strategy to further reduce the effect of fatigue. It has shown good

reproducibility and may detect glaucomatous progression earlier than a standard strategy, albeit at the expense of accuracy (Bengtsson and Heijl, 1998). The presence of cataract prevents comparison of results in individuals following multifocal intraocular lens implantation for perimetry and imaging, however, contact lenses give a reasonable approximation for possible effects in an individual (Hunkeler 2002). The limitations to using contact lenses to approximate intraocular lenses include disruption to the tear film (Lopez-Gil 2002, Ho 2003), lens flexure (Lopez-Gil 2002, Ho 2003) and rotation (Guirao 2001) varying the optical effect, different optical principles for creating multifocality and potential damage to the lenses from inappropriate handling by the patients (Cho 2013). Lopez-Gil (2002) and Ho (2003) assessed the impact of tear film and lens flexure on optical degradation and found little effect, however, Lopez-Gil reported that the aberration impact of a contact lens varied on the eye and the subjects assessed were younger so therefore probably had better tear quality.

Aychoua et al. (Aychoua et al., 2013) assessed the influence of a multifocal intraocular lens on SAP using SITA standard 30-2 test using monofocal and phakic age-matched controls. The results showed a reduction in MD for the multifocal intraocular lens subjects for size III and V targets; however, the results were potentially confounded by inherent differences between the subject groups and possible fatigue effects. A recent study to determine the effect of the multizone Acuvue Bifocal CL (Vistakon, Inc., Jacksonville, FL, USA) versus monofocal contact lenses on 24-2 standard SITA SAP found a reduction in MD (Madrid-Costa et al., 2012). The study did not compare results for specific zones, evaluate fatigue effects or assess image quality of digital photographs taken through the lenses. The current UK diabetic screening program relies on fundus photographs for remote screening and photographs are examined and graded, with primary, secondary and arbitration grading depending on the observer's expertise. Computerised digital analysis may replace the labour-intensive examination of photographs by screeners, as it has proved to be a very effective and sensitive

alternative (Ockrim and Yorston 2010), so it is important to assess for any potential effects of multifocal lenses on photographic image quality. This current study aims to address this deficit in knowledge.

7.2 Study aim

This was a prospective, cross-over and single-masked trial. The objective of the study was to evaluate the effect of wearing a high addition Air Optix™ Aqua Multifocal (AOAM) on the Humphrey field analyser SITA fast 30-2 perimetry in comparison to a single vision contact lens, Softens Daily Disposable (Bausch & Lomb), to correct their near vision. Digital images of the fundi of the same subjects through both lenses were obtained using the Topcon Non-Mydriatic Retinal Camera (Topcon Medical Systems, Inc., Oakland, NJ, USA). These were compared by the same person (SM) using visual inspection.

7.2.1 Sample size

A pilot study of 5 participants (mean age 34 ±14 years) was conducted to evaluate the effect of wearing a high addition Air Optix™ Aqua Multifocal (AOAM) on the Humphrey field analyser SITA fast 30-2 perimetry in comparison to a single vision contact lens, Softens Daily Disposable (Bausch & Lomb). The sample size was calculated based on the pattern standard deviation measurements (1.34 ±0.16 vs. 1.55 ± 0.22) using G*Power 3 (Faul et al., 2007) and a sample of 10 subjects was required. Twelve were recruited to allow for drop-out.

7.2.2 Subjects

The study was conducted at Aston University and the subjects were recruited by the same investigator (SM) from the optometry public service clinics. All the subjects had been seen within 3 months of the study for a complete eye examination, which included refraction, tonometry, visual field screening, slit lamp biomicroscopy, and examination of the fundus. Ten of the participants habitually wore contact lenses and an additional

spectacle prescription for reading. One subject additionally wore Acuvue Bifocal Contact Lenses (Vistakon, Inc., Jacksonville, FL, USA), a centre distance design, on a part time basis. The exclusion criteria were: aged <40 years, unable to handle contact lenses and lens care products, 0.30 logMAR or worse distance VA in each eye, ametropia greater in sphere than -6.50D or +5.50D with astigmatism of >-0.75D (corneal vertex =14mm), unwilling to use the habitual lens care product for trial period, requiring concurrent ocular medication, eye injury or surgery within twelve weeks immediately prior to enrolment for this trial, pre-existing ocular irritation that would preclude contact lens fitting, currently enrolled in an ophthalmic clinical trial, evidence of systemic or ocular abnormality, infection or disease likely to affect successful wear of contact lenses or use of their accessory solutions, known sensitivity to any of the study solutions, is pregnant or nursing, irregular astigmatism or monovision.

7.2.3 Experimental procedure

Trial contact lenses and materials

The subjects were all fitted with the lenses detailed in Table 6.1. The power of the single vision Soflens daily disposable contact lens was calculated to correct their mean spherical equivalent prescription plus the recommended addition for the Humphrey visual Screener. The mean spherical equivalent power was used to calculate the distance power for the Air Optix™ Aqua Multifocal 'HI' addition lens.

Table 7.1 Contact lens details for single vision and multifocal lenses.

	Single vision contact lens	**Multifocal Contact lens**
Name	SofLens Daily Disposable	AIR OPTIX™ AQUA MULTIFOCAL
Description	Single Vision SCL	Progressive SCL
Design	Aspheric	Aspheric
Material	Hilafilcon B	Lotrafilcon B
Coating	None	Plasma coated
Water content	59%	33%
Base curve	8.60	8.60
Diameter	14.20	14.20
Spherical Rx available for trial	-9.00 to +6.50D in 0.25D steps, 0.50D above -6.50	-6.00 to +6.00D in 0.25D steps
Add available for trial	None	LOW; MED and HI
Storage solution	Poloxamine-containing solution	Isotonic phosphate buffered saline
Labelling	Commercial foil on blister	Commercial foil on blister

Procedure and data collection

The study followed the tenets of the Declaration of Helsinki and informed consent was obtained by having the subject read, sign and date the Informed Consent Form (prior to any trial related evaluations or procedures). The ethical committee of Aston University

approved the study and subjects were free to withdraw at any time without obligation. This experiment was conducted concurrently with the multifocal contact lens trial (Chapter 5). The demographic information such as subject's gender and age was collected and the subject's visual acuity (VA) measured following refraction using loose lenses and a trial frame at 12mm BVD. The best corrected visual acuity was measured using an EDTRS chart for distance and a decimal reading chart for near (supplied by the JENVIS Research Institute at the University of Applied Sciences in Jena, Germany). Keratometry measurements were taken and a slit lamp biomicroscopy evaluation performed, including the use of sodium fluorescein dye, to assure that the subject had no signs of any acute ocular infections, injuries, or other abnormalities that would prohibit participation or discontinuation from the trial. The experimental procedure involved taking the subject in to the room where the visual field screener was located and seating them in front of the screener. The investigator (SM) inserted a contact lens in to each eye and dimmed the lights so the subject was unaware of which contact lens they were wearing. The order of testing through the different lens types was randomised. A patch was placed over one eye and the patient had a practice attempt at the field test. After a rest of at least 5 minutes, the subject completed their visual field test, the first eye varying according to a randomisation table. If the criteria for reliability was not met (fixation losses > 20% and false positive and false-negative errors >33% (Heijl, 1987)), the tests were repeated either later that day or at the next visit.

Following the visual field test, the subject was asked to place their chin on the chin rest of the digital camera and look at the red light. The first eye photographed was always the same as the first eye tested on the field screener. The camera was set to fire automatically when the retinal image was in focus. The patient was asked to wait for at least five minutes so their pupils had time to increase in size again and the image for the other eye was taken.

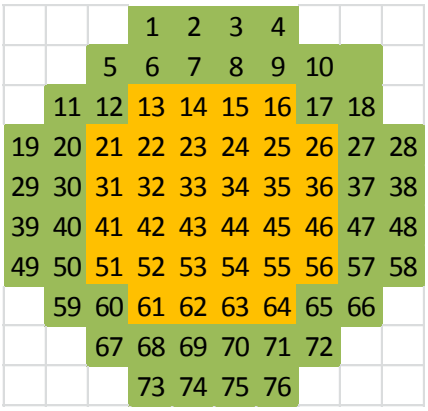
7.2.4 Randomisation

A randomisation table was generated to assign the order of the contact lenses worn for the field test and photographs.

7.2.5 Statistical analysis

The global indices provided by the Humphrey software were analysed due to the common use of these values in practice. The mean deviation values are adjusted for age and weighted for eccentricity, so the mean sensitivity was also calculated from raw sensitivity values excluding the blind spot (location 36 and 46) as indicated in Figure 6.1. A subset of locations within 20° of fixation (indicated in orange in Figure 6.1) and points between 21-30° (indicated in green in Figure 6.1) were also explored.

Figure 7.1 Grid showing separate zones for analysis (RE represented). Points within 20° of fixation are indicated in orange and points between 21-30° in green. Locations 36 and 46 were excluded from the analysis.



Statistical analysis was performed with SPSS v20.00 (SPSS Inc, Chicago,IL, USA). Normality of the data from the visual field test was assessed using the Shapiro-Wilk test and as the significance value was greater than 0.05, the paired sample t-test was used to compare the means. Pearson's correlation was used to give an indication of

effect size. The photographs were compared by visual inspection, specifically the relative calibre of blood vessels and optic disc and macular features.

7.3 Results

A total of 10 subjects (4 male, 6 female) aged between 49-60 years, mean ± SD: 52.1 ± 3.5 years, participated in the study. Two further subjects could not give a reliable field plot despite several attempts and were excluded. Twenty eyes of 10 participants were evaluated and all visual field examinations satisfied the reliability criteria. Reliability indices were compared for each type of lens and the results are summarised below.

Table 7.2 Mean visual acuities in subjects wearing multifocal contact lenses. Visual acuity data was not collected for single vision lenses.

	Distance visual acuity measured in logMAR	**Near visual acuity measured in decimal**
Right eye	0.06 ± 0.10	0.56 ± 0.16
Left eye	0.06 ± 0.11.	0.53 ± 0.14

Table 7.3 Visual field reliability parameters. Fixation losses are out of 11 where there was no fixation loss and 12 where there was 1 or more fixation loss.

	Single vision contact lens	**Multifocal contact lens**	**p**
Time (minutes)	3.36 ± 0.35	3.47 ± 0.307	<0.01
Fixation losses	0.85 ± 0.81	1.15 ± 0.87	0.22
False negative (%)	0.25 ± 1.11	1.05 ± 2.64	0.19
False positive (%)	1.5 ± 2.56	2.8 ± 3.34	0.17

Significant results for the Shapiro Wilk test were obtained for all visual field reliability parameters and so the Wilcoxon signed-rank test was used to compare the data.

The time taken to complete the visual field test was approximately 6 seconds longer with the multifocal contact lens (median = 3.44) than the single vision contact lens (median = 3.23), z = -2.875, p = <0.01, r = -0.64. The number of fixation losses was similar with both lenses (median = 1 for both lenses), z = -1.222, p = 0.22. There were slightly more false positives for the multifocal lens (median = 1.5), than the single vision lens (median = 0) although this failed to reach statistical significance, z = -1.366, p = 0.17. False negatives were similar for each lens type (median = 0 both lenses), z = -1.289, p = 0.19.

The fatigue effect was assessed by comparing the time taken for the first and second eyes. On average, the second eye took slightly longer than the first, although this was not statistically significant; single vision lenses, first eye: mean = 3.30 ± 0.377, median = 3.18, second eye: mean = 3.42 ± 0.322, median = 3.36, z = -1.290, p = 0.19. For the multifocal lens, first eye: mean = 3.40 ± 0.14, median = 3.45 and for the second eye mean = 3.57 ± 0.45, median 3.45, z = 1.186, p = 0.24.

The results for mean sensitivity were normally distributed and were compared by paired t-test. On average, participants had a higher MS using single vision contact lenses (Mean= 29.52, SD = 0.96) than multifocal contact lenses (Mean = 28.49, SD = 1.00). T (21) = -4.707, p = <0.01, r = 0.51. The results for mean deviation were higher with the multifocal contact lenses (mean = -1.30, SD = 1.08) than the single vision contact lenses (Mean = -0.19, SD = 0.90). T (21) = -4.495, p = <0.01, r = 0.49. There was no significant difference for PSD between the multifocal contact lenses (Mean = 1.522, SD = 0.23) and single vision contact lenses (Mean = 1.40, SD = -0.22), T = 0.432, p = 0.67.

Figure 7.2 The number of defect symbols in the total deviation visual field plot for multifocal versus single vision contact lenses.

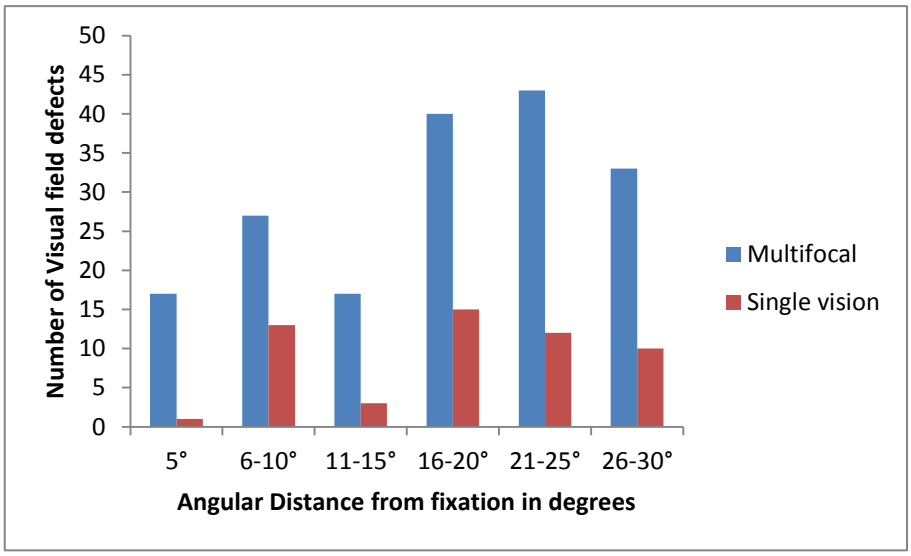
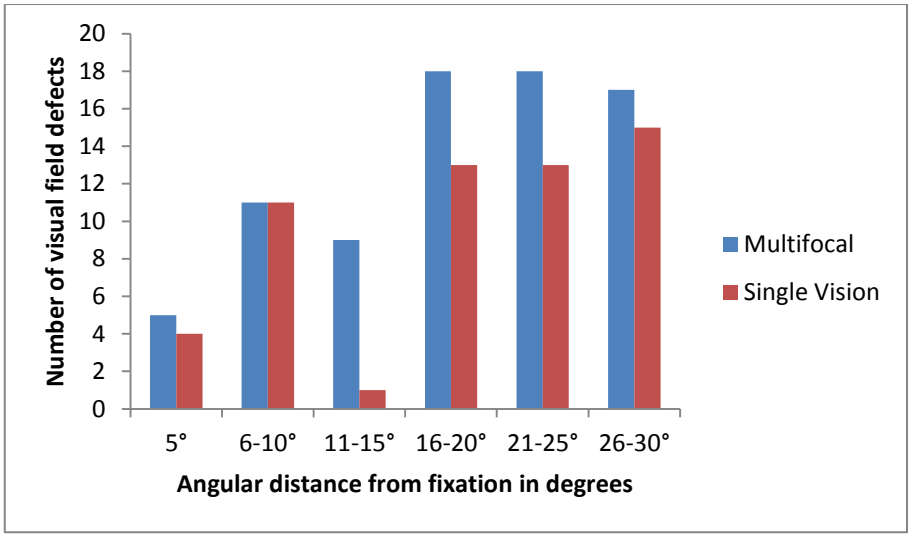


Figure 7.3 The number of defect symbols in the pattern deviation visual field plot for multifocal versus single vision contact lenses.



Comparisons were also made between the 30 points lying within 20° of fixation and the 44 points lying between 21 and 30° of fixation. For the points within 20°, the mean sensitivity was greater for single vision contact lenses (Mean = 31.15, SD = 1.07) than multifocal contact lenses (Mean = 29.86, SD = 0.911). Similar results were found for the peripheral points (Mean single vision contact lenses = 28.40, SD = 1.09, Mean multifocal contact lenses = 27.56, SD = 1.14). There was no obvious difference in

image quality between the photographs taken through the single vision contact lens and the photographs taken through the multifocal contact lens when assessed by visual inspection. There was no evidence of distortion or magnification effects; the calibre of the blood vessels appeared identical and features of the disc and macula were equally clear in all images. There were veiling reflections, possibly arising from the tear film or ocular media, however, these effects were found in both lens types and were unlikely to be as a result of the multifocality.

Table 7.4 Comparison for MS visual field results for peripheral versus central points between single vision contact lenses and multifocal contact lenses.

	t	**p**	**r**
Points within 20° fixation	-4.05	0.001	0.44
Points between 21-30° fixation	-5.12	<0.001	0.50

Table 7.5 Field plots for subject describing '3D' effect through multifocal contact lens compared to single vision contact lens.

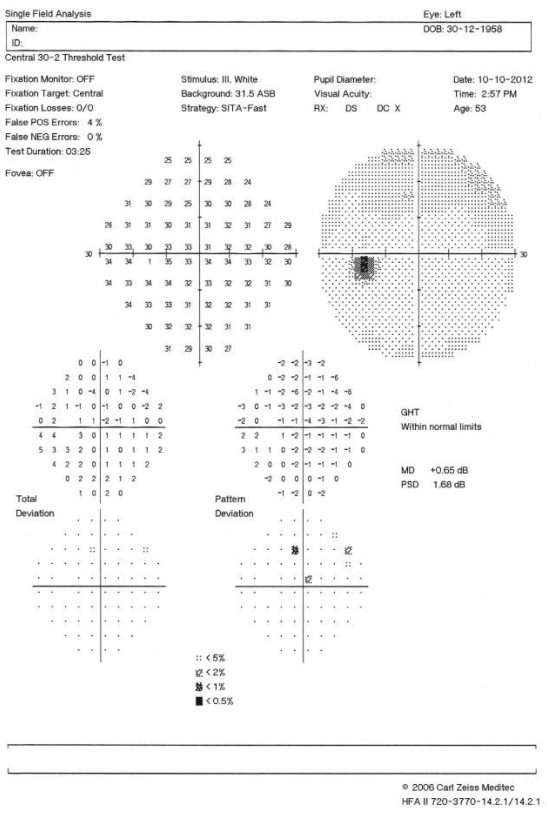
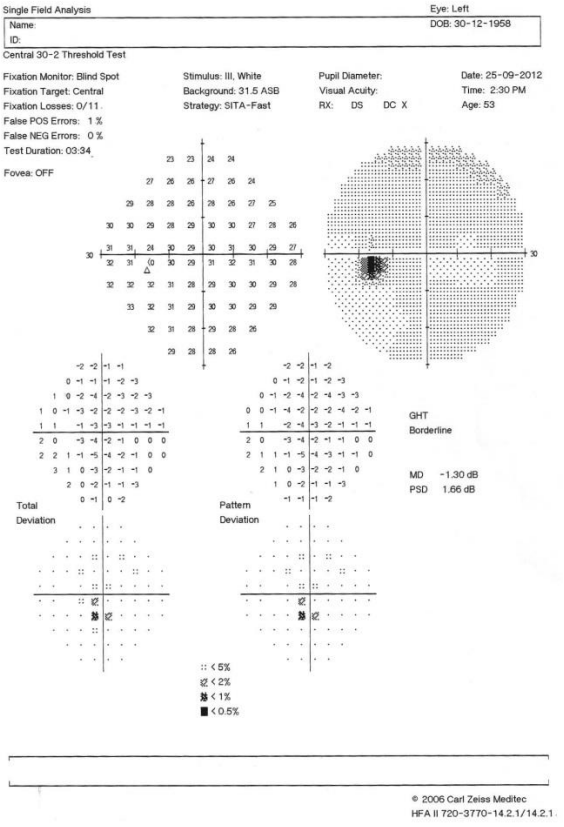
LE Single vision contact lens	LE Multifocal contact lens
	

Table 7.6 Visual field plots of successful multifocal contact lens subject showing comparison with single vision lens.

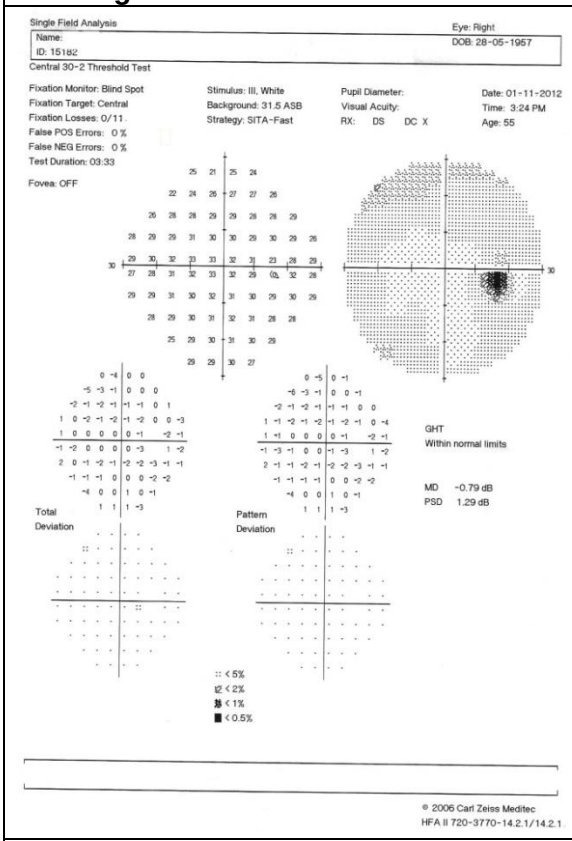
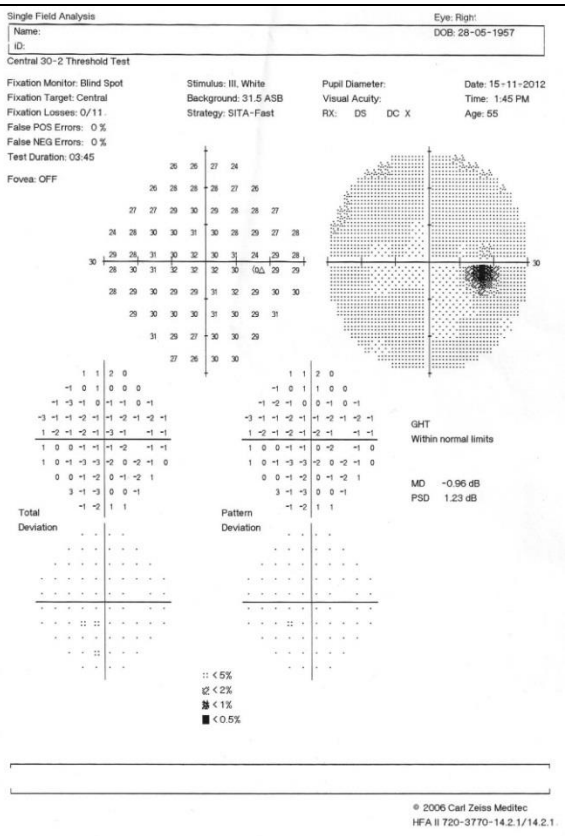
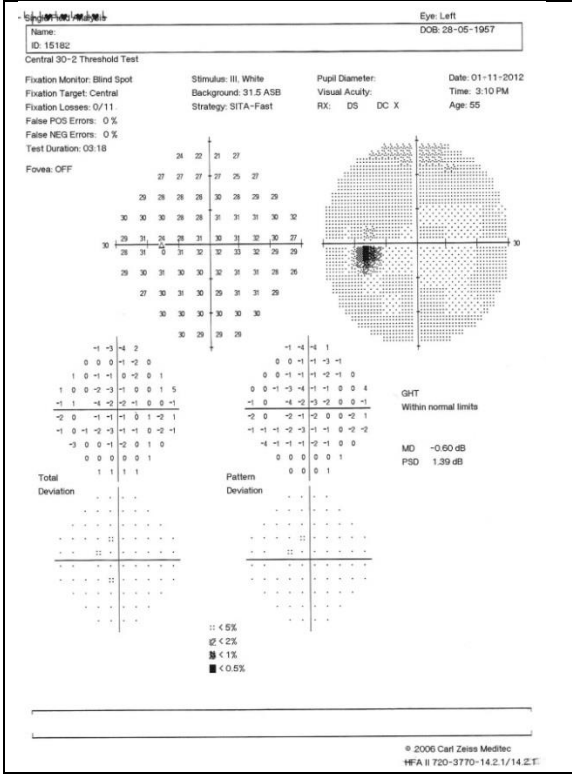
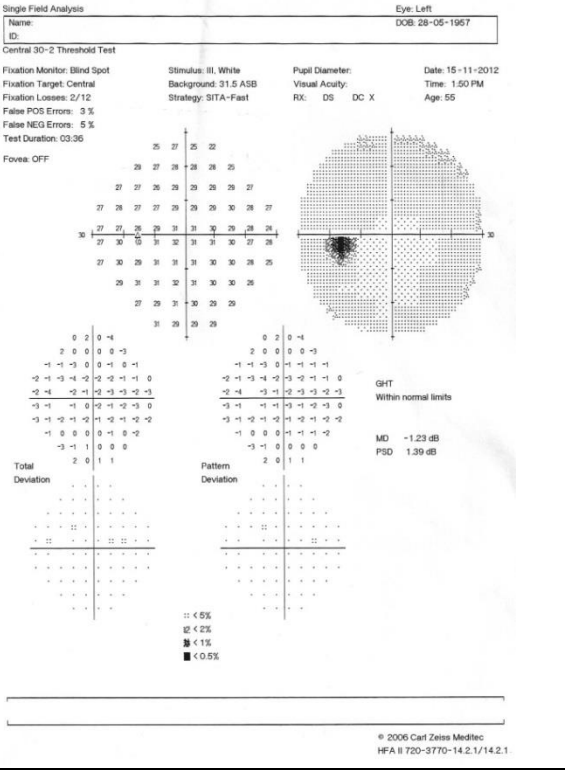
RE Single vision contact lens	RE Multifocal contact lens
	
LE Single vision contact lens	**LE Multifocal contact lens**
	

Table 7.7 Visual field plot of multifocal contact lens subject with typical reductions in mean deviation and pattern standard deviation as compared to single vision values.

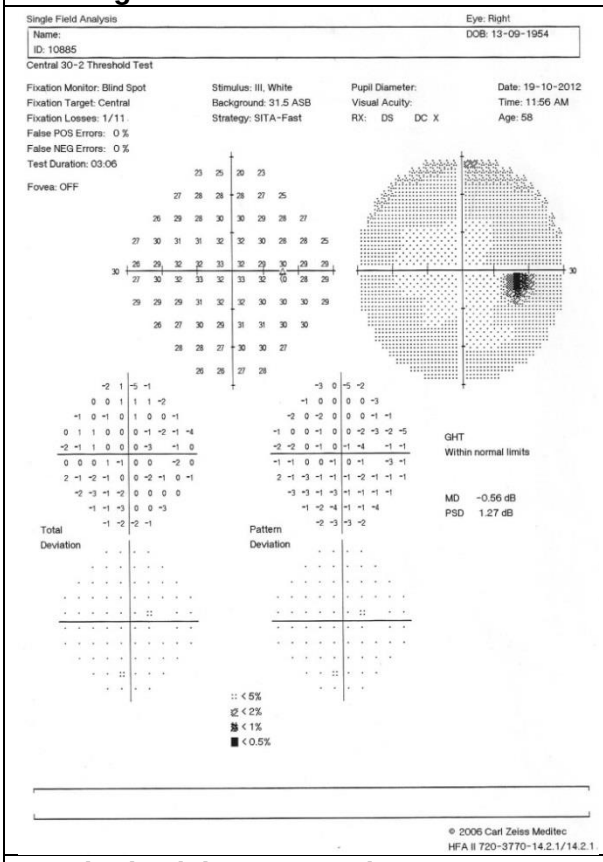
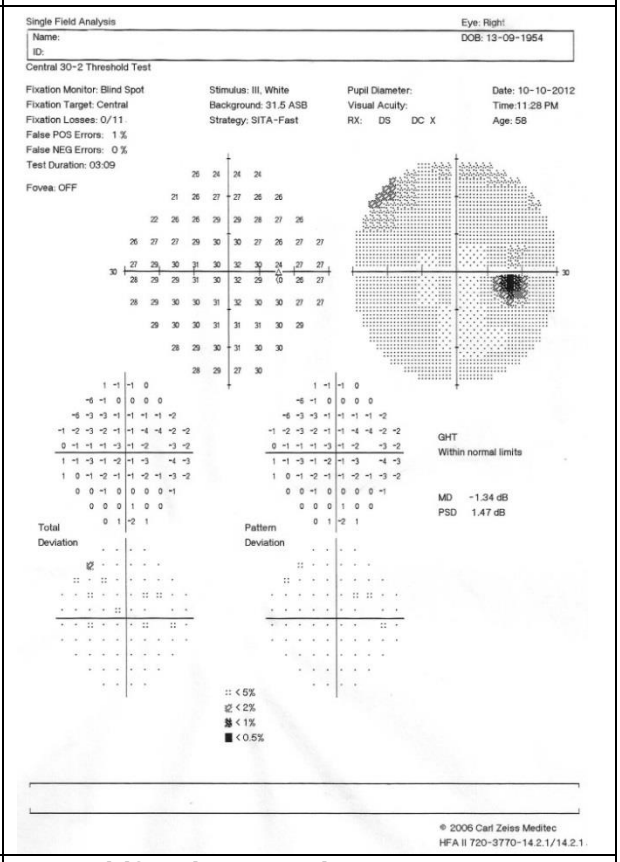
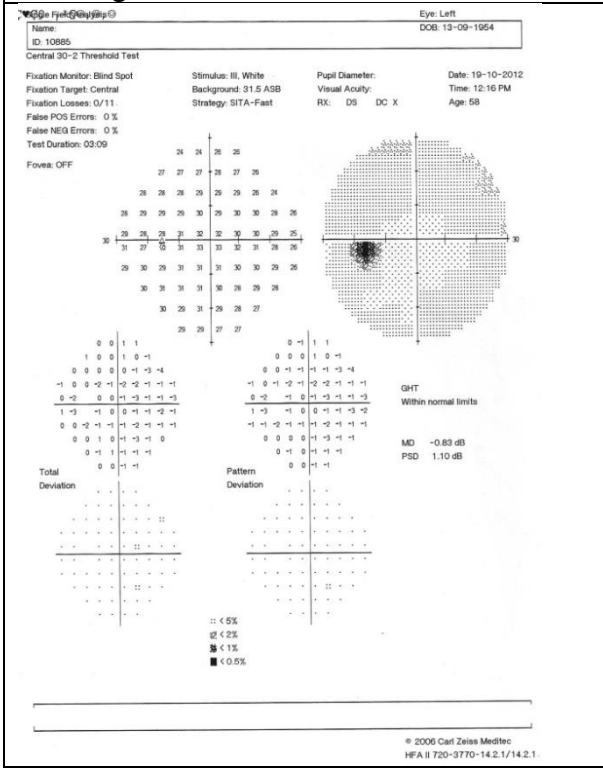
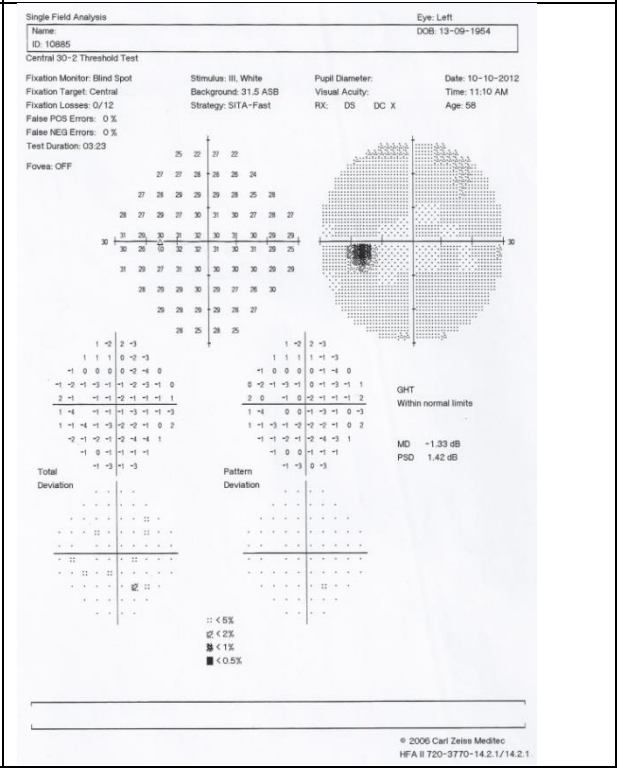
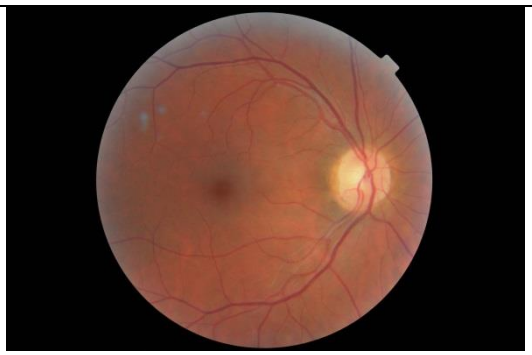
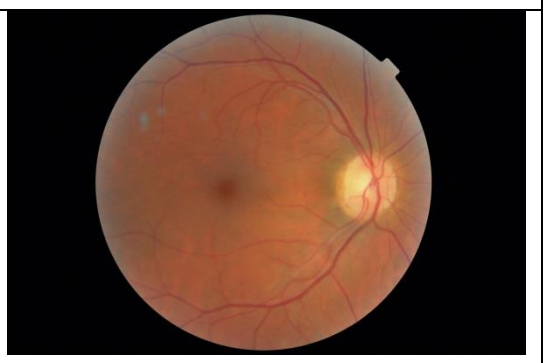
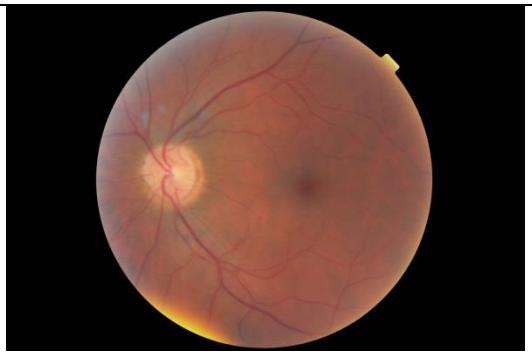
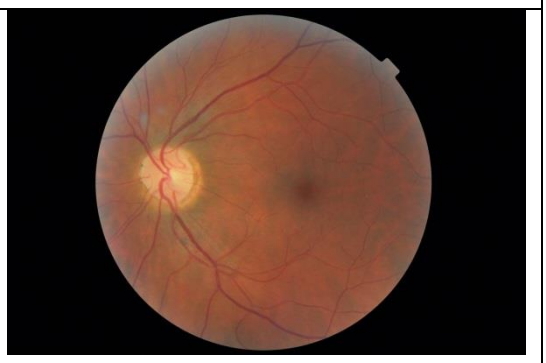
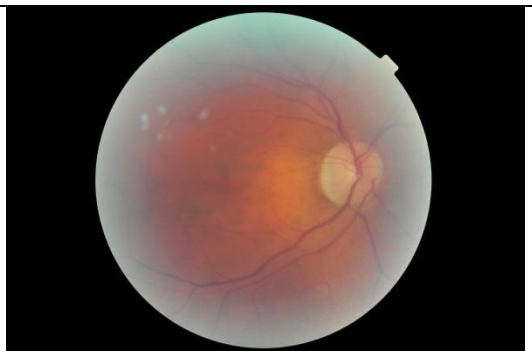
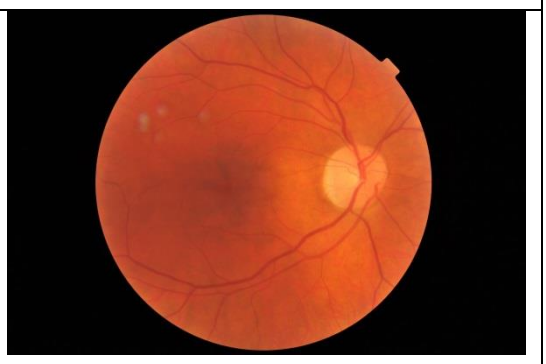
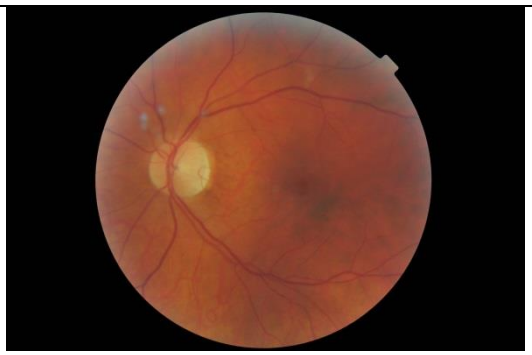
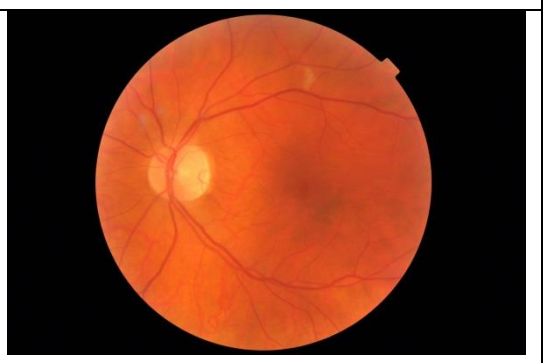
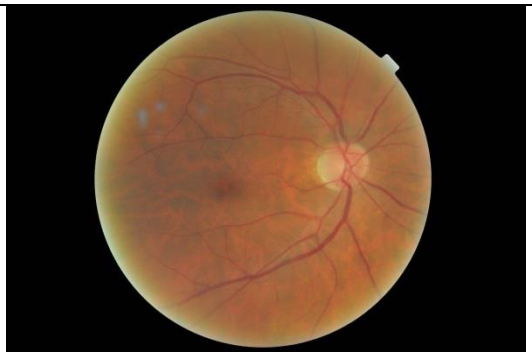
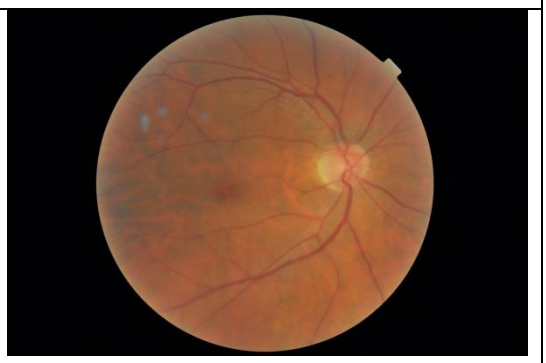
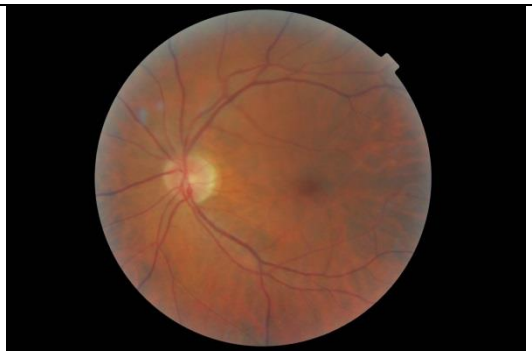
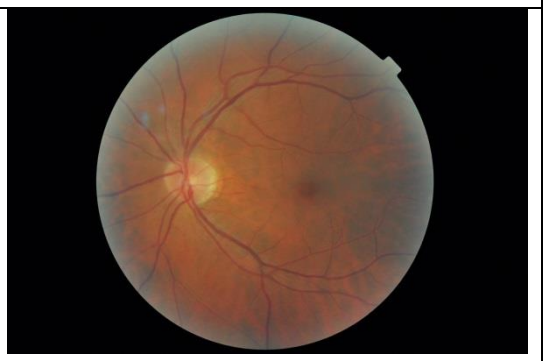
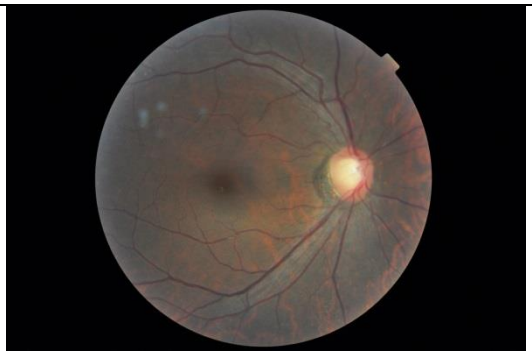
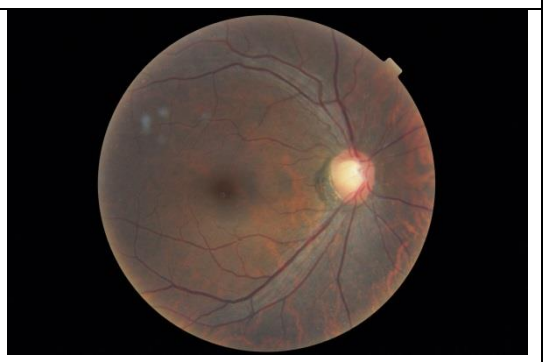
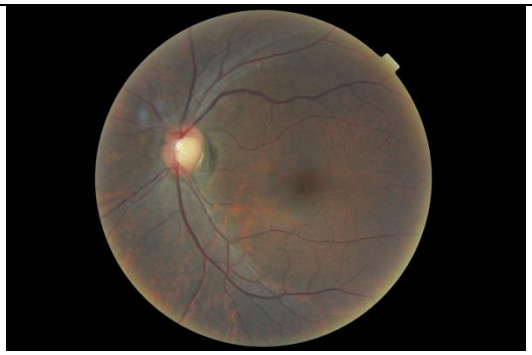
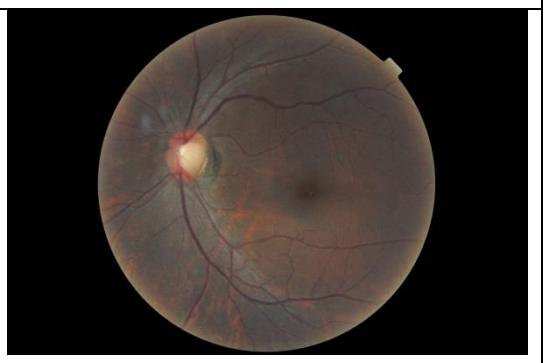
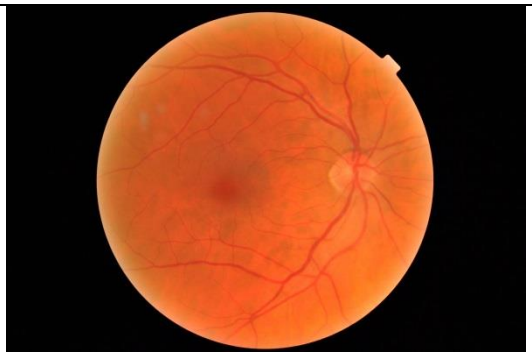
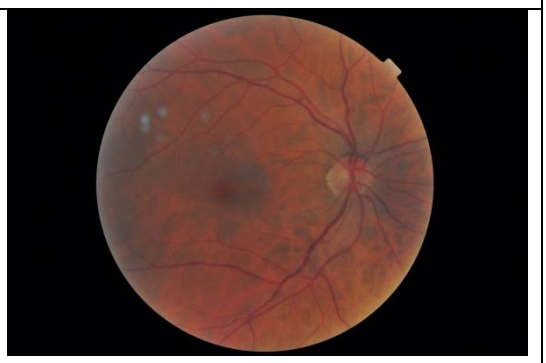
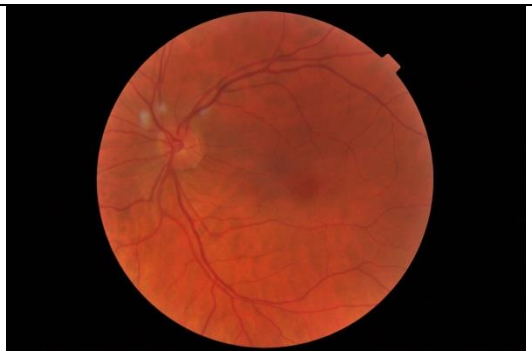
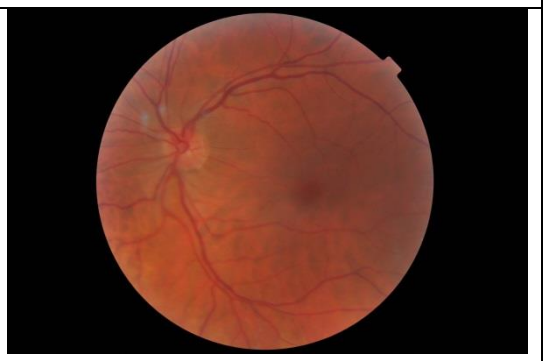
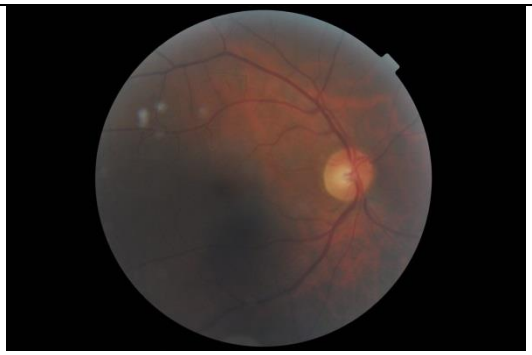
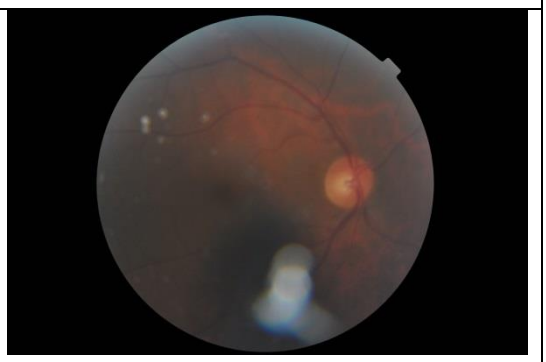
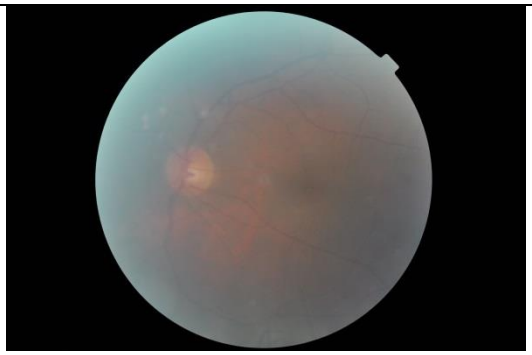
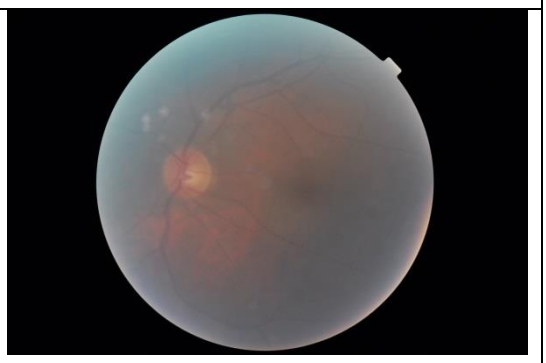
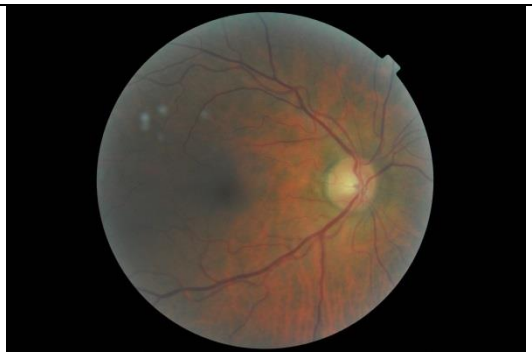
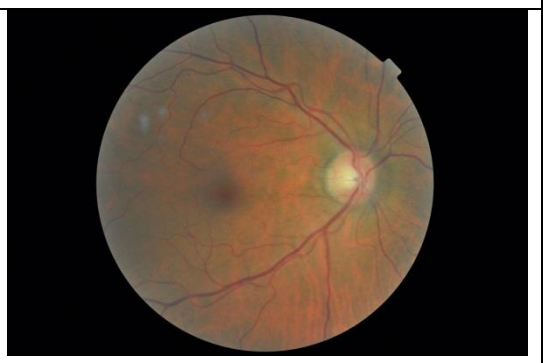
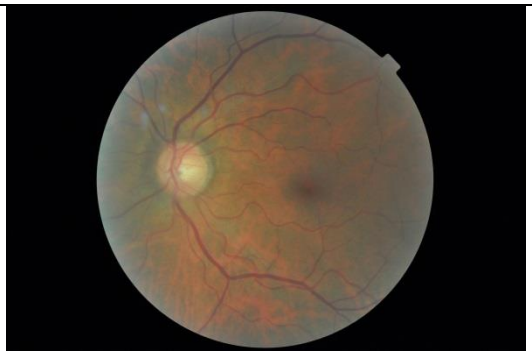
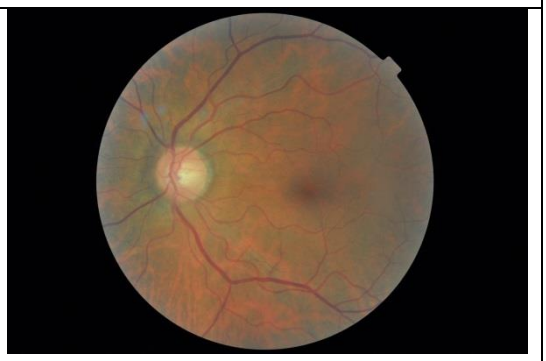
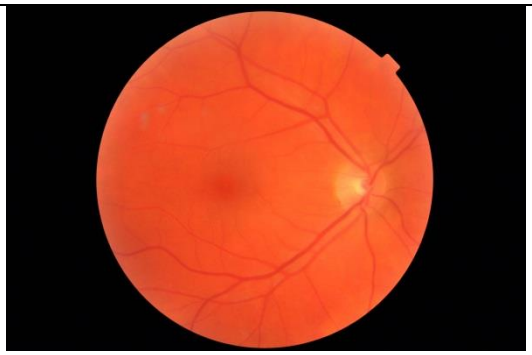
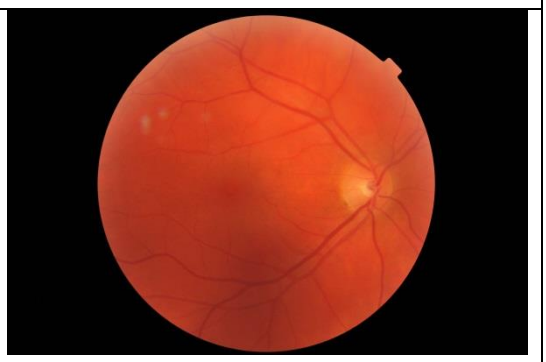
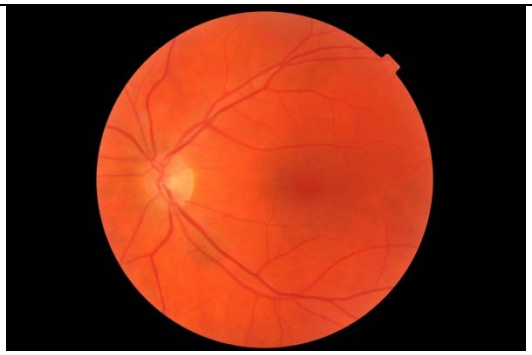
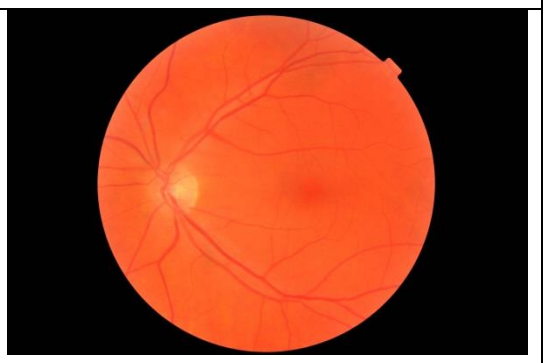
RE Single vision contact lens	RE Multifocal contact lens
	
LE Single vision contact lens	**LE Multifocal contact lens**
	

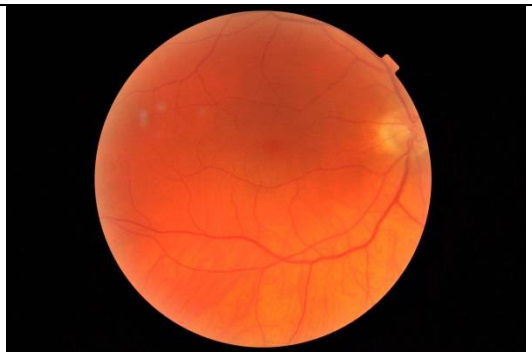
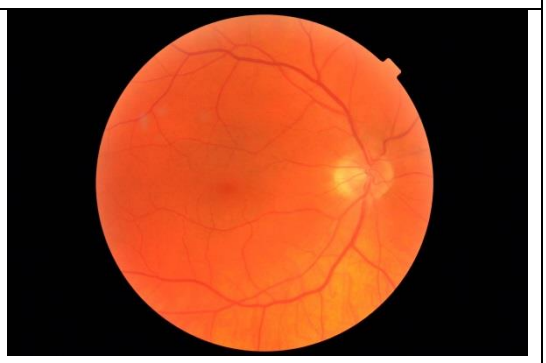
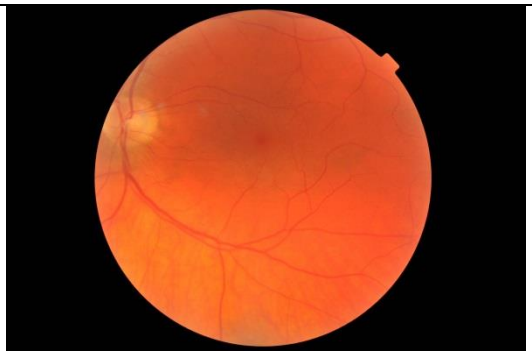
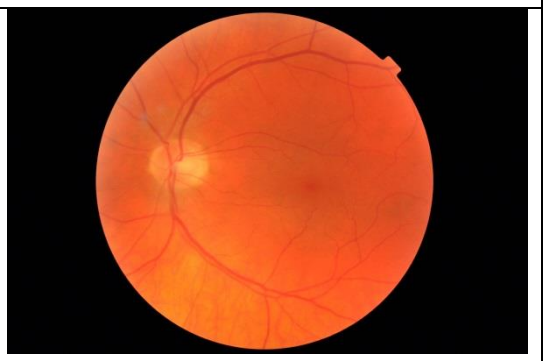
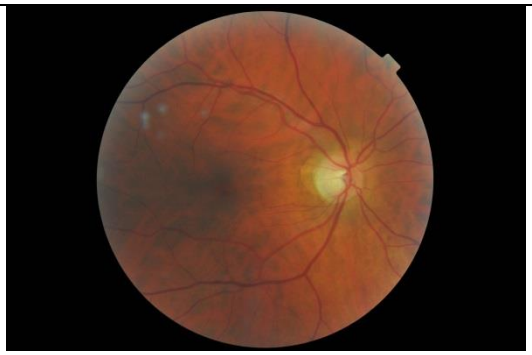
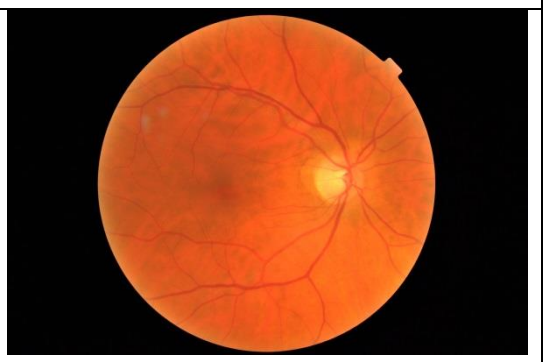
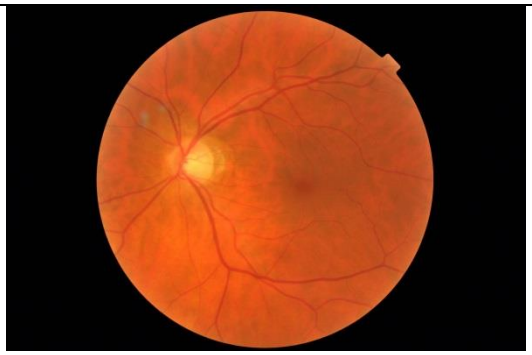
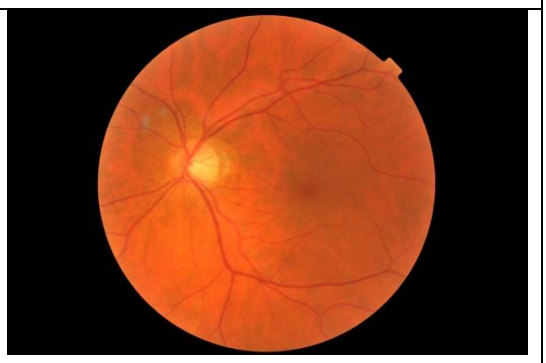
Table 7.8 Comparison of digital images taken with the Topcon Digital Camera through single vision contact lenses and multifocal contact lenses.

Subject Number	Single vision contact lens	Multifocal contact lens
1 (RE)		
1 (LE)		
2 (RE)		
2 (LE)		

Subject Number	Single vision contact lens	Multifocal contact lens
3 (RE)		
3 (LE)		
4 (RE)		
4 (LE)		

Subject Number	Single vision contact lens	Multifocal contact lens
5 (RE)		
5 (LE)		
6 (RE)		
6 (LE)		

Subject Number	Single vision contact lens	Multifocal contact lens
7 (RE)		
7 (LE)		
8 (RE)		
8 (LE)		

Subject Number	Single vision contact lens	Multifocal contact lens
9 (RE)		
9 (LE)		
10 (RE)		
10 (LE)		

7.4 Discussion

The subjects took significantly longer to complete the visual field test when wearing the multifocal contact lens than with the single vision lens ($p = <0.01$). Madrid-Costa et al. also found increased test times for the multifocal contact lens; however, the difference did not reach significance in their study (Madrid-Costa et al., 2012). With the multifocal contact lens there were more complaints about losing focus on the central fixation point, the test had to be repeated more frequently and although the difference in the reliability indices were not statistically significant, the values for all the reliability indices were generally worse. The fatigue effect as measured by the length of time taken to complete the field test with the second eye versus the first (Hudson et al., 1994) was not significant when the subjects were wearing either type of lens. This was useful information as it meant the differences in the results were more likely to be due to the multifocality of the lens rather than inattention or fatigue, which can be a factor in the standard strategies (Montolio et al., 2012). It is unclear whether this was the case in comparative studies (Aychoua et al., 2013, Madrid-Costa et al., 2012) as their designs did not allow for this assessment.

The mean deviation reflects the overall depression in the visual field and the mean results for the multifocal contact lens (-1.30dB) were significantly more depressed ($p = < 0.01$) than for the single vision contact lens (-0.19dB). The MD values for both lenses were closer to zero than the Madrid-Costa et al. study (Madrid-Costa et al., 2012), which were -2.98dB for the multifocal contact lens and -2.01dB for the single vision contact lens (this may be due to the patient's own sensitivity, although the age ranges were similar), however, the differences between multifocal contact lens and single vision contact lens MD in both studies are similar, which Madrid-Costa et al. attributed to reduced contrast sensitivity caused by 'a lower amount of light energy available at each one of the focal points' (Madrid-Costa et al., 2012). Expanding on this, a zonal multifocal contact lens such as the Acuvue bifocal design has been associated with

ghosting and halos and the centre-distance design is adversely affected by smaller pupils (Ardaya et al., 2004), both of which could reduce sensitivity during perimetry. The patient's own higher order aberrations have been shown to affect the visual quality at near for aspheric multifocal lens designs, particularly with centre near designs such as Air Optix Multifocal (Martin and Roorda, 2003), effectively reducing contrast sensitivity and increasing the MD. The field plot through the multifocal lens for a subject who commented that their near vision 'looked like it was in 3-D' in the left eye, is shown compared to the results for the single vision contact lens in Table 6.5. This is interesting because the high contrast near acuity was better in the left eye (0.5) than the right (0.4) and yet the poor visual quality put the result in to the 'borderline' category for the glaucoma hemisphere test (GHT).

Aychoua et al found a 2.72dB reduction in MD in the subjects with multifocal intraocular lenses versus those with aspheric monofocal intraocular lenses in an older demographic of subjects. The increase in HOAs with age is well documented and the issue of compatibility of these increased higher order aberrations and the particular multifocal intraocular design could possibly explain this. Table 6.9 shows the field plot of a 70 year old female patient who recently underwent bilateral cataract surgery and implantation of multifocal intraocular lenses (4/12 post-operative). She described the right eye as 'perfect', but the left as 'slightly fuzzy,' despite similar high contrast acuities for distance and near. The undilated pupil sizes were 6.06mm for the right eye and 5.48mm for the left. Aberrometry using the Nidek OPD-Scan III across 5.4mm natural pupils revealed a difference in higher order aberrations, specifically higher levels of coma and total spherical aberrations, which may account for the reduced image quality. The photographs taken with the Topcon Non-Mydriatic Retinal Camera showed no distortion (Figure 6.4).

Table 7.9 Visual field plots of 70 year old subject with multifocal intraocular lenses.

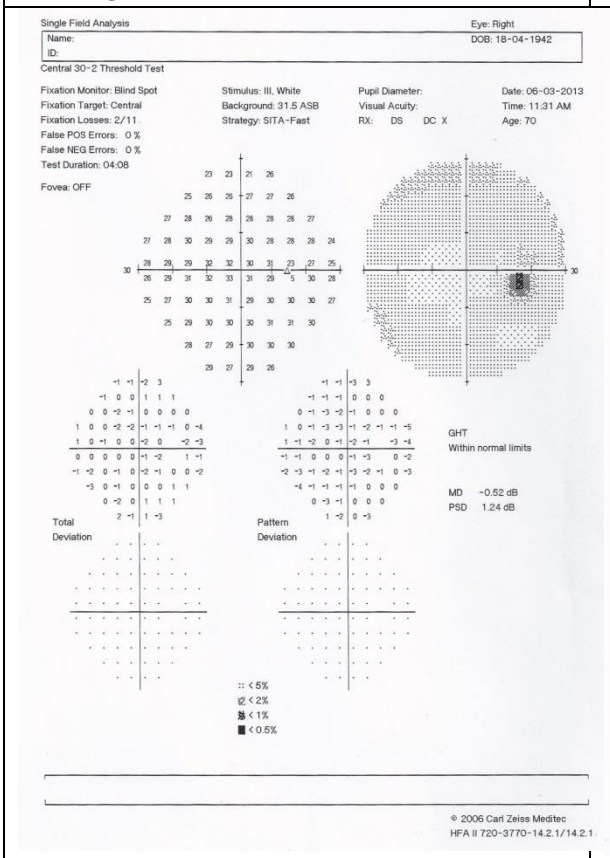
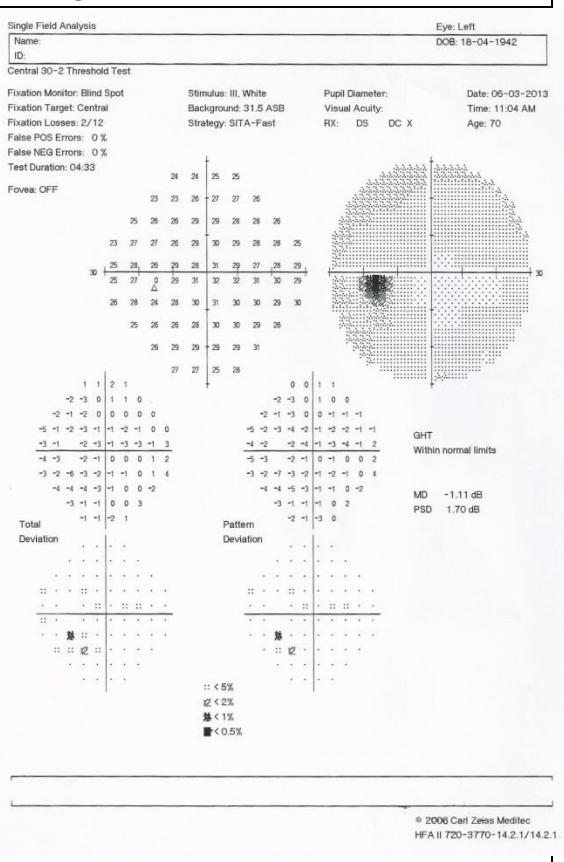
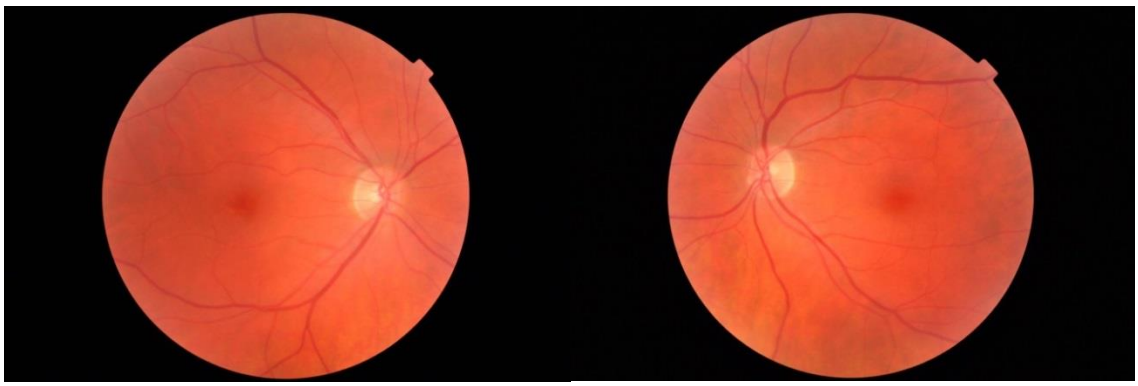
RE MIOL	LE MIOL
	

Table 7.10 Results for aberrometry across 5.4mm pupil in 70 year old subject with bilateral aspheric multifocal intraocular lenses.

	Right Eye	**Left Eye**
Total aberrations (µm)	1.194	1.137
Coma (µm)	0.205	0.478
Trefoil (µm)	1.048	0.907
Total spherical aberrations (µm)	0.072	0.103

Figure 7.4 Digital images taken through aspheric multifocal intraocular lenses in 70 year old subject.



Mean sensitivity (MS) was also compared, which are the raw sensitivity values with no adjustment for age or weighting for eccentricity (Dr Robert Cubbidge, personal communication). There was a reduction of 1.03dB in sensitivity for the multifocal contact lens ($p = < 0.01$), although no comparison was possible with Madrid-Costa et al. (2012) as they did not assess this metric. The difference between values for MS obtained when subjects wore the multifocal contact lenses versus single vision lenses (1.03dB) is less than the difference in MD (1.11dB), however, the lack of adjustment in the figures as mentioned previously could account for this. Aychoua et al. only provided median values for MS; however, they also found a significantly higher value for MS in the group with single vision aspheric intraocular lenses versus the group with multifocal intraocular lenses (Aychoua et al., 2013).

There was no significant difference for PSD between the multifocal intraocular lens (Mean = 1.522, SD = 0.23) and single vision contact lens (Mean = 1.40, SD = -0.22), $T = 0.432$, $p = 0.67$. This was similar to the Madrid-Costa et al. study who found the mean PSD for multifocal contact lenses to be 1.49dB and for single vision contact lenses 1.52dB, $p= 0.32$ (Madrid-Costa et al., 2012). Aychoua et al. found no significant differences in PSD for multifocal intraocular lenses versus monofocal intraocular lenses, however, this group went on to investigate 7 test locations within 10°

eccentricity and 8 test locations outside 10° eccentricity. Madrid-Costa et al. (2012) did not compare performance in zones in their experiment, but our choice of the 30-2 SITA fast program enabled us to compare inner and outer zones. The MS was higher for single vision contact lenses than the multifocal contact lenses by 1.29dB, p = <0.01 in the points within 20° eccentricity and by 0.84dB, p = <0.01 in the points 21-30° eccentricity. This indicates that the multifocal contact lenses are having a larger effect on the central 20°, which is contrary to the multifocal intraocular lens study where they found similar differences between somewhat fewer locations inside and outside 10° (Aychoua et al., 2013) and therefore warrants further investigation.

The number of significantly depressed points as indicated by defect symbols was compared for multifocal versus single vision lenses. This was assessed in zones according to eccentricity to aid identification of an annular defect or ring scotoma. For MD and PSD there were consistently more defects, mainly at the P<5% value, when subjects wore the multifocal contact lens, particularly from 16-30°.Peripheral points tend to be less reliable when assessed by perimetry, however, there was a difference between the multifocal and single vision contact lens so this anomaly warrants further investigation.

Generally if there was difficulty obtaining an image, it was through both types of contact lens, particularly in subjects with a greasier tear film combined with a smaller pupil. In these cases the image produced was obscured by reflections, despite being taken in a room with no other light source. The automatic function on the camera frequently readjusted for one or two minutes before taking the image through the multifocal contact lens. When an image was captured there were no obvious distortions or artefacts, however, this may be due to software autocorrecting for any mild variations in focus across the image. The images taken through the multifocal intraocular lenses were obtained without difficulty.

This study used both eyes of each subject because in a clinical situation eyes are often compared to establish normality for an individual and it enabled an assessment of fatigue effect. The use of both eyes in the statistical analysis, however, may have led to an increase in Type 1 error as the eyes are not statistically independent. The pupil size may have been a factor in the results as for the Madrid-Costa study using Acuvue Bifocal CL (Madrid-Costa et al., 2012), however, their study used a centre distance design where the pupil size was more critical for adequate near vision. The reflections noted during photography from the contact lens and the influence of the tear film on the surface of the lens was not thought to interfere with the visual field results as the effect was noticed on both lens types. The use of contact lenses to approximate intraocular lenses has limitations; the tear film can be adversely affected, decreasing visual quality (Tutt 2000), the lenses can decentre introducing higher-order aberrations and they are based on different designs to produce the near addition power (Charman and Saunders 1990).

The clinical consequences of the reduced MD and increased probability symbols may lead clinicians to erroneously conclude there are early signs of glaucomatous field loss, particularly in the presence of borderline pressures. It has been estimated that the thresholds in the SITA fast algorithms tend to overestimate the actual threshold by 2.18dB when compared to standard strategies (Bengtsson and Heijl, 1998); however, clinicians tend to look at the probability symbols and the Glaucoma Hemifield Test (GHT) rather than absolute values for each point. The results here suggest that multifocality may mask changes on the PSD, particularly if they fall between 16-30°, therefore this may be of concern and requires investigation, preferably in groups with early glaucomatous field loss to evaluate this effect.

7.5 Conclusion

Multifocal contact lenses and intraocular lenses are designed to maximise vision when the patient is binocular, so any test assessing the eyes individually is confounded by reduced individual acuity and visual quality. This needs to be considered when conducting perimetric screening of individuals with multifocal contact lenses or intraocular lenses, as baseline values may be altered in a normal eye. Digital photographic image capture through a multifocal lens appears to be unchanged.

7.6 Summary

This chapter showed how multifocal lenses can alter the perimetric sensitivity values in normal eyes, although the effect on photographic images was imperceptible. The following chapter discusses the implications of findings for the experimental chapters, including improvements and future work.

Chapter 8 DISCUSSION AND CONCLUSIONS

8.1 Summary

This body of work has initially attempted to demonstrate how new technology is capable of increasingly accurate and repeatable results when characterising the refractive state of the eye, and how technology used to create interventions has improved outcomes, resulting in improved visual quality from the patient's and clinician's perspectives. However, the human eye has inherent aberrations that do not allow a perfect image to be formed on the retina and is particularly affected by spherical aberration. Spherical aberration varies with the radial distance from the centre of the pupil, so while the eye may have no refractive error in the centre of the pupil, there is an increasing error in the annular zones surrounding the pupil centre. The resultant image may be sharp for small pupil diameters but degrade as the pupil expands. In other words, an eye with excessive spherical aberration forms its image in the proper location, but the image itself is not necessarily "good."

Higher order aberrations can arise from the tear film, cornea, lens or the ocular media and have the effect of confounding potential optical or surgical solutions for vision correction. Tear instability can precipitate optical disturbances resulting in reduction of visual quality commonly reported by dry eye patients (Goto et al., 2002), contact lens wearers (Richdale et al., 2007) and post-refractive surgery patients (Shoja and Besharati, 2007). The importance of this symptom is underlined by its recent inclusion in the definition of dry eye (Lemp, 2007). The lubricants study did not show any significant differences for visual quality with different lubricants in normal or border-line dry eyes; however, more work is required to understand the dynamic of the lipid layer in the presence of excess aqueous. This would particularly apply to patients with dry eye symptoms who also suffer from epiphora and poor tear quality, and would be best investigated with a temporal measure of lipid quality combined with concurrent visual

quality monitoring. The effects of the tear film on visual quality can be compounded when multifocal contact or intraocular lenses are also in place.

Effective simultaneous vision is required with multifocal modes of correction which rely on the required image being in focus while the out-of-focus image is reduced to a broad low frequency background image. In reality the patient's own ocular higher order aberrations dictate how focussed the required image is and in some cases this may mean the difference in image quality between the 'in-focus' and 'out-of-focus' image are not sufficiently disparate to allow effective suppression. Pupil size (Han et al., 2012) and lens decentration (Holladay et al., 2002) (a more changeable variant in contact lenses) also play a key role in the quality of the image, however, additional factors e.g. previous refractive surgery (Khoramnia et al., 2012) or concurrent disease processes such as glaucoma (Teichman et al., 2012) may complicate matters. The Stiles-Crawford effect has been shown to significantly improve defocused image quality and vision in low lighting conditions (Zhang et al., 1999), however this effect does not apply to patients who have had myopic refractive laser surgery, particularly with a small optic zone or those with a previously high prescription and therefore a steeper surrounding corneal annulus. This is because the steeper locus deflects incoming light and increases the chances of detection by rods which have minimal directional sensitivity or cones due to the smaller angle of incidence (Brown, 2009). Therefore patients who wish to have MIOL will need careful consideration to maintain acceptable visual quality under reduced ambient lighting conditions.

In the glaucomatous eye, a reduction in contrast sensitivity, specifically at mesopic levels, is correlated with visual field loss and the disease preferentially affects contrast sensitivity as compared with visual acuity (Hawkins et al., 2003). However, cataract also independently reduces visual acuity and contrast sensitivity and so patients with both conditions may benefit from aspheric monofocal (Trueb et al., 2009) intraocular lenses which control for spherical aberration and have been shown to improve mesopic

and scotopic contrast sensitivity, or even aspheric multifocal intraocular lenses (Dexl et al., 2013), which in non-glaucomatous eyes resulted in contrast sensitivity levels within normal limits for age (Hohberger et al., 2007). This current study demonstrated that visual field changes measured through a multifocal contact lens showed a detrimental change in MD and therefore new values may need to be calculated for patients with multifocal lenses. Changes to the visual field as a result of corneal modification or multifocal lenses may mask early glaucomatous changes in some individuals and requires further investigation, particularly in patients who had surgery in the early phases of both technologies. This is of particular concern in patients who have developed comorbidities such as cardiovascular disease or diabetes. Further work may clarify the extent to which patients that underwent refractive surgery with small ablation zones, particularly with higher corrections, may be affected regarding their choice of intraocular lenses, and the implications for screening and treatments should ocular disease occur.

Neural changes which occur with age may actually reduce the impact of anterior eye anomalies. The modulation transfer function describes how different spatial frequencies are transmitted through the eye; there is a cut off frequency value (which increases as the pupil increases) after which no spatial frequency can pass. The loss of high spatial frequencies means the loss of information about the details of an object, which causes decreased image quality and could affect visual acuity. With increased age the pupil gets smaller and although the effects of higher order aberrations are reduced, the effects of diffraction are increased. It has been demonstrated that the effects of pupil size are noticed to a different degree depending on the task, as lower spatial frequencies carry information sufficient for many routine perceptual activities such as face perception and visual stabilisation of posture (Ginsburg, 1978). At lower light levels, contrast is reduced; higher spatial frequencies become invisible and perception of objects depend on detecting more global features. It has been shown that older

persons have more difficulty performing routine perceptual activities in low contrast environments, although this has been linked to neural rather than optical factors (Owsley et al., 1981). The introduction of additional aberrations through dry eye, refractive laser surgery, multifocal contact or intraocular lenses could compound this problem.

Multifocal dominant design contact lenses are able to change the peripheral refractive profile in emmetropic eyes increasing relative peripheral myopia. Lenses with a +3.00D add power create significant peripheral myopisation (Lopes-Ferreira et al., 2011). Koller et al. investigated the effect of refractive errors on peripheral visual field (30-50°) thresholds in automated static perimetry. Hyperopic eyes showed a significant influence of refraction at 30° and a reduction of 0.4dB per dioptre. Myopic eyes showed a 0.75dB decrease in sensitivity for 30°, 0.46dB decrease for 40° and 0.22dB decrease for 50° (Koller et al., 2001) This is important when considering field plots from patients fitted with zonal multifocal intraocular lenses of centre distance design e.g. Array and AMO Rezoom and refractive surgery patients with small ablation zones, who will probably be affected by this phenomenon.

In terms of imaging, there were no defects apparent on images obtained through multifocal lenses. This is particularly relevant to diabetic retinopathy screening as global prevalence of diabetic retinopathy is currently estimated at 35% (Yau et al., 2012). Retinal measurements using OCT have shown artefacts through multifocal IOLs and retinal measurements using OCT after myopic LASIK showed statistically significant increases in total macular volume attributed to changes in corneal curvature, although high myopia (Rauscher et al., 2009) and axial length (Savini et al., 2012) have also been shown to affect retinal nerve fibre layer measurements by OCT. Establishing ‘normal’ parameters for anterior eye anomalies is important to establish guidelines for interpretation of results.

7.2 Limitations

The use of both eyes for some of the experiments within this thesis, whilst failing to exploit the between eye correlation, may have caused a lack of statistical power. A paired t test was chosen when including both eyes, however, this procedure was unlikely to yield accurate results due to reduced standard errors, which was more likely to give a significant ‘p’value and imprecise confidence intervals. The true variance between eyes within a population would have been greater than suggested by the number of eyes included in that particular sample, and may therefore have resulted in a type 1 error (Armstrong 2013). This may have been the case for the Nidek OPD-Scan III validation, the laser surgery studies and the perimetry studies. An alternative could have been to randomly select one eye for inclusion. However, selecting just right eyes as in the lubricants experiment also introduced bias as the sample does not fully represent all eyes, rather characteristics of right eyes in a population. There are ethical concerns regarding taking measurements and not using them for inclusion as the patient has been subjected to unnecessary procedures. Alternative procedures could have been to analyse the data from each eye separately or average the readings, however, in the case of the refractive surgery study, the laser ablation would not have been identical in each eye and therefore it would have been better to correct for correlation (Armstrong 2013).

The effects of dry eye on visual quality in more severe cases is well established, however, this current study demonstrated that in a self-diagnosed population of marginal dry eye, the patient perceived a benefit even in the absence of objective changes. The increased use of computers in all workplaces has undoubtedly led to an increase in dry eye symptoms and as patients are also likely to self-medicate, it is important to evaluate interventions singly and in combination in these marginal groups to be able to offer appropriate advice. Foulks (2003) identified the placebo effect as a confounding factor in many trials of new ocular lubricants and this seems to be the

case here as almost every subject reported improvement for lubricants singly and in combination. The Nidek OPD-Scan III maps more points than previous versions and so is more able to characterise what is actually happening to the wavefront, however, it would have been useful to have the osmolarity readings as originally intended in this experiment to correlate the findings or possibly assist with the grouping at the beginning of the experiment. Aberrometry was only possible over a 5mm pupil size for the lubricant experiment as the room was light, however, over a 6mm pupil the differences may have been more pronounced and possibly correlated with the normal and dry eye groupings. It would have been more useful to perform aberrometry in a dim room and then taken the results off the aberrometer for a smaller pupil size to assess the possible visual effects in normal lighting conditions. Measurements more frequently, perhaps every 10 minutes, would also have given more information regarding the duration of effects for lubricants and possibly shown a point where the groups differed, however, the students were in assessments so this was not possible. It was important to use a group of subjects who were in the same environment for all test conditions and for that reason the compromises were the frequency of measurement and the lighting. It would be interesting to repeat the experiment on a cohort with diagnosed dry eyes, possibly allowing a small gap between application of drop and spray, when used in combination, to allow the excess to drain away. Closer measurement intervals or a continuous measurement system would be sensible in this case, as the effects of lubricants would most likely be of a much shorter duration in dry eye.

The study investigating the effects of refractive laser surgery on army personnel raised several issues. The initial expectations were that army personnel were capable of high levels of concentration and would give reliable responses; however, the levels of fatigue or general anxiety within this cohort had not been anticipated. The group were possibly more anxious than the usual surgery candidate as they all required high

standards of acuity to remain active and even though they were not always using their refractive appliances (contact lenses and spectacles) in the field, they had no documented evidence to say their vision was not at an acceptable level, which would not be the case following the surgery. It was not possible to assess the effect of laser refractive surgery on vision using night vision goggles as was originally hoped because the subjects all used different models. Under low resolution conditions, it has been shown that tasks requiring low spatial frequencies were more tolerant to defocus; and for dilated pupils, the lower the frequency, the larger the increase in depth of focus (Legge et al., 1987). This could possibly explain why some of the soldiers had managed wearing no correction with night vision goggles prior to surgery. We had anticipated a larger number of recruits, however, of the volunteers coming forward, there were several who were unsuitable for treatment due to the type of refractive error or who were not eligible for funding. This meant the power of the study was severely compromised and it could only realistically be considered exploratory rather than fully descriptive. A larger cohort with a wider range of refractive errors and a comparative treatment would be needed to fully characterise the visual quality for LASEK using a solid state laser.

Different pupil sizes give different visual effects with multifocal contact lenses and multifocal intraocular lenses and therefore pupillometry would have given useful information for the studies in Chapters 5 and 6. A study by Artigas et al. compared a refractive multifocal intraocular lens with 2 hybrid refractive–diffractive multifocal intraocular lenses and found no significant difference in performance for large pupil sizes. However, with small pupils and for distance vision the image quality was somewhat worse with the refractive–diffractive IOLs than with the purely refractive IOL. For near vision, the image quality with the hybrid IOLs was better than with the refractive IOL at all pupil sizes (Artigas et al., 2007). This could have a potential effect on visual field screening for patients fitted with refractive multifocal IOLs. A more recent

study evaluating a diffractive multifocal intraocular lens has shown that higher aberrations have a significant effect for pupils over 5mm (Han et al., 2012).

Obtaining reliable visual fields was also an issue for all of the studies examining perimetry data. It may be useful to investigate the visual field using astandard automated perimetry and an additional measure such as the multifocal electroretinogram (mfERG), particularly in patients treated with refractive laser surgery to correct their vision that have developed glaucoma. Although mfERG requires co-operation from the patient to maintain steady fixation, it requires no decision making and therefore may provide useful additional information (Tafreshi et al. 2010).

The main difficulty encountered during the experimental work was finding suitable cohorts and therefore the measurements were either not sensitive enough or the differences were masked by too much noise to reach significance. This was particularly true for the lubricant experiment in Chapter 3 and when assessing differences in visual fields in Chapters 4 and 6. There were, however, individual sets of results where there were clearly visual effects and future work should concentrate on assessing groups with more similar characteristics e.g. eyes with diagnosed dry eyes or laser surgery patients with small or similar ablation zones and/or higher prescriptions.

7.3 Conclusions

The expectations of patients are ever increasing as technology improves and the standard eye examination has evolved to include increasingly sophisticated tests. Technology has also improved understanding of disease and healing processes and there is a move away from tests requiring experienced personnel to conduct and interpret them to more objective and automated procedures. There are increasing options to remain spectacle free at all ages with the development of new refractive laser surgery techniques, multifocal contact lenses and multifocal and accommodating intraocular lenses. The ubiquitous use of computer and mobile telephone displays has

changed our visual requirements and therefore the need for high visual quality at multiple distances is possibly the start of a trend, where instead of being seen as a ‘lifestyle’ choice, sophisticated optical or even surgical solutions will be considered a basic necessity. In a society with a rapidly increasing life expectancy and more access to better health care, the chances of multiple procedures and age-related, or in some cases disease-related complications confounding the results of these procedures are more likely. This body of work has attempted to understand these processes as individual events and work will hopefully continue to explore the effects of interventions in combination.

References

Al-Ghoul, K. & Costello, M. 1997. Light microscopic variation of fiber cell size, shape and ordering in the equatorial plane of bovine and human lenses. *Molecular Vision,* 3(2),1-5.

Al-Mezaine, H. S. 2010. Descemet's membrane detachment after cataract extraction surgery. *International Ophthalmology,* 30(4)**,** 391-396.

Altinors, D. D., Akça, S., Akova, Y. A., Bilezikçi, B., Goto, E., Dogru, M. & Tsubota, K. 2006. Smoking associated with damage to the lipid layer of the ocular surface. *American Journal of Ophthalmology,* 141(6)**,** 1016-1021.

Amann, J., Holley, G. P., Lee, S.-B. & Edelhauser, H. F. 2003. Increased endothelial cell density in the paracentral and peripheral regionsof the human cornea. *American Journal of Ophthalmology,* 135(5)**,** 584-590.

Anderson, I., Sanders, D. R., van Saarloos, P. & Ardrey IV, W. J. 2004. Treatment of irregular astigmatism with a 213 nm solid-state, diode-pumped neodymium: YAG ablative laser. *Journal of Cataract & Refractive Surgery,* 30(10)**,** 2145-2151.

Anderson, N. J. & Edelhauser, H. F. 1999. Toxicity of ocular surgical solutions. *International Ophthalmology Clinics,* 39(2)**,** 91-106.

Andley, U. P. 2007. Crystallins in the eye: Function and pathology. *Progress in Retinal and Eye Research,* 26(1)**,** 78-98.

AOP 2009. Royal Navay Vision Standards available at: http://www.aop.org.uk/uploads/uploaded_files/royal_navy_vs.pdf, accessed September 27th 2013.

Applegate, R. A., Ballentine, C., Gross, H., Sarver, E. J. & Sarver, C. A. 2003a. Visual acuity as a function of Zernike mode and level of root mean square error. *Optometry & Vision Science,* 80(2)**,** 97-105.

Applegate, R. A., Marsack, J. D., Ramos, R. & Sarver, E. J. 2003b. Interaction between aberrations to improve or reduce visual performance. *Journal of Cataract & Refractive Surgery,* 29(8)**,** 1487-1495.

Armstrong, R. A. (2013). Statistical guidelines for the analysis of data obtained from one or both eyes. *Ophthalmic and Physiological Optics*, *33*(1), 7-14.

Ardaya, D., DeVuono, G., Lin, I., Neutgens, A., Bergenske, P., Caroline, P. & Smythe, J. 2004. The effect of add power on distance vision with the Acuvue bifocal contact lens. *Optometry-Journal of the American Optometric Association,* 75(3)**,** 169-174.

Artigas, J. M., Menezo, J. L., Peris, C., Felipe, A. & Díaz-Llopis, M. 2007. Image quality with multifocal intraocular lenses and the effect of pupil size: Comparison of refractive and hybrid refractive–diffractive designs. *Journal of Cataract & Refractive Surgery,* 33(12)**,** 2111-2117.

Atchison, D. A., Collins, M. J., Wildsoet, C. F., Christensen, J. & Waterworth, M. D. 1995. Measurement of monochromatic ocular aberrations of human eyes as a function of accommodation by the Howland aberroscope technique. *Vision Research,* 35(3)**,** 313-323.

Austin, M. W., Sreekantam, S., Martin, S. & Hill, R. J. 2006. Bilateral ring scotomas following laser in situ keratomileusis. *Journal of Cataract and Refractive Surgery,* 32(6)**,** 1062-1064.

Aychoua, N., Junoy Montolio, F. & Jansonius, N. M. 2013. Influence of multifocal intraocular lenses on standard automated perimetry test results. *JAMA Ophthalmology*, 131(4), 481-485.

Aydin, B., Cagil, N., Erdoğan, S., Erdurmus, M. & Hasiripi, H. 2008. Effectiveness of laser-assisted subepithelial keratectomy without mitomycin-C for the treatment of high myopia. *Journal of Cataract & Refractive Surgery,* 34(8)**,** 1280-1287.

Azar, D. T., Chang, J.-H. & Han, K. Y. 2012a. Wound Healing After Keratorefractive Surgery: Review of Biological and Optical Considerations. *Cornea,* 31 Suppl 1 **,** S9-S19.

Azartash, K., Kwan, J., Paugh, J. R., Nguyen, A. L., Jester, J. V. & Gratton, E. 2011. Pre-corneal tear film thickness in humans measured with a novel technique. *Molecular Vision,* 17**,** 756-767.

Baek, T. M., Lee, K. H., Kagaya, F., Tomidokoro, A., Amano, S. & Oshika, T. 2001. Factors affecting the forward shift of posterior corneal surface after laser in situ keratomileusis. *Ophthalmology,* 108(2)**,** 317-320.

Bailey, M. D. & Zadnik, K. 2007. Outcomes of LASIK for myopia with FDA-approved lasers. *Cornea,* 26(3)**,** 246-254.

Bakaraju, R. C., Ehrmann, K., Falk, D., Ho, A. & Papas, E. 2012. Optical performance of multifocal soft contact lenses via a single-pass method. *Optometry & Vision Science,* 89(8)**,** 1107-1118.

Baudouin, C., Labbé, A., Liang, H., Pauly, A. & Brignole-Baudouin, F. 2010. Preservatives in eyedrops: the good, the bad and the ugly. *Progress in Retinal and Eye Research,* 29(4)**,** 312-334.

Begley, C. G., Chalmers, R. L., Abetz, L., Venkataraman, K., Mertzanis, P., Caffery, B. A., Snyder, C., Edrington, T., Nelson, D. & Simpson,T. 2003. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Investigative Ophthalmology and Visual Science,* 44(11)**,** 4753-4761.

Bellucci, R., Morselli, S. & Piers, P. 2003. Comparison of wavefront aberrations and optical quality of eyes implanted with five different intraocular lenses. *Journal of Refractive Surgery,* 20(4)**,** 297-306.

Bellucci, R., Scialdone, A., Buratto, L., Morselli, S., Chierego, C., Criscuoli, A., Moretti, G. & Piers, P. 2005. Visual acuity and contrast sensitivity comparison between Tecnis and AcrySof SA60AT intraocular lenses: A multicenter randomized study. *Journal of Cataract & Refractive Surgery,* 31(4)**,** 712-717.

Bengtsson, B. & Heijl, A. 1998. SITA Fast, a new rapid perimetric threshold test. Description of methods and evaluation in patients with manifest and suspect glaucoma. *Acta Ophthalmologica Scandinavica,* 76(4)**,** 431-437.

Bengtsson, B. & Heijl, A. 2000. False-negative responses in glaucoma perimetry: indicators of patient performance or test reliability? *Investigative Ophthalmology and Visual Science,* 41(8)**,** 2201-2204.

Benjamin, W. J. 1993. Simultaneous vision contact lenses: Why the dirty window argument doesn't wash. *International Contact Lens Clinic,* 20**,** 239-242.

Bennett, E. S. 2008. Contact lens correction of presbyopia. *Clinical and Experimental Optometry,* 91(3)**,** 265-278.

Berdy, G. J., Abelson, M. B., Smith, L. M. & George, M. A. 1992. Preservative-free artificial tear preparations: assessment of corneal epithelial toxic effects. *Archives of Ophthalmology,* 110(4)**,** 528-532.

Berger, J. S., Head, K. R. & Salmon, T. O. 2009. Comparison of two artificial tear formulations using aberrometry. *Clinical and Experimental Optometry,* 92(3)**,** 206-211.

Bissen-Miyajima, H., Minami, K., Yoshino, M., Nishimura, M. & Oki, S. 2010. Autorefraction after implantation of diffractive multifocal intraocular lenses. *Journal of Cataract & Refractive Surgery,* 36(4)**,** 553-556.

Bland, J. M. & Altman, D. G. 1986. Statistical methods for measuring agreement between two methods of clinical measurement. *The Lancet,* 1(8476)**,** 307-310.

Boote, C., Dennis, S., Newton, R. H., Puri, H. & Meek, K. M. 2003. Collagen fibrils appear more closely packed in the prepupillary cornea: optical and biomechanical implications. *Investigative Ophthalmology & Visual Science,* 44(7)**,** 2941-2948.

Bourne, R. R., Minassian, D. C., Dart, J. K., Rosen, P., Kaushal, S. & Wingate, N. 2004. Effect of cataract surgery on the corneal endothelium: modern phacoemulsification compared with extracapsular cataract surgery. *Ophthalmology,* 111(4)**,** 679-685.

Bron, A. J., Smith, J. A. & Calonge, M. 2007. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *The Ocular Surface,* 5(2)**,** 108-152.

Bron, A. J., Tripathi, R. & Tripathi, B. 1997. Wolff's Anatomy of the Eye and Orbit. 8th edition. London: Chapman & Hall.

Brown, S. M. 2009. Stiles-Crawford effect revisited: Considerations for refractive surgery. *Journal of Cataract & Refractive Surgery,* 35(4)**,** 792-794.

Brown, S. M., Bradley, J. C., Xu, K. T., Chadwick, A. A. & McCartney, D. L. 2005. Visual field changes after laser in situ keratomileusis. *Journal of Cataract & Refractive Surgery,* 31(4)**,** 687-693.

Brown, S. M. & Morales, J. 2002. Iatrogenic ring scotoma after laser in situ keratomileusis. *Journal of Cataract and Refractive Surgery,* 28(10)**,** 1860-1863.

Bullimore, M. A., Fusaro, R. E. & Adams, C. W. 1998. The repeatability of automated and clinician refraction. *Optometry & Vision Science,* 75(8)**,** 617-622.

Buscemi, P. 2004. Retinoscope double pass aberrometry: principles and application of the Nidek OPD-Scan. *Wavefront Customized Visual Correction: The Quest for Super Vision II. Thorofare, NJ: Slack Inc***,** 149-53.

Camellin, M. & Wyler, D. 2008. Epi-LASIK versus epi-LASEK. *Journal of Refractive Surgery,* 24(1)**,** S57-63.

Chalita, M. R., Meng, X. & Krueger, R. R. 2003. Correlation of aberrations with visual symptoms using wavefront analysis in eyes after laser in situ keratomileusis:

Commercially approved wavefront-quided custom ablation: First year in review. *Journal of Refractive Surgery,* 19(6)**,** S682-S686.

Chalmers, R. L., Begley, C. G. & Caffery, B. 2010. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Contact Lens and Anterior Eye,* 33(2)**,** 55-60.

Charman, W.N. 2005. Aberrations and myopia. *Ophthalmic and Physiological Optics,* 25(4)**,** 285-301.

Charman, W. N. (2008). The eye in focus: accommodation and presbyopia. *Clinical and Experimental Optometry*, *91*(3), 207-225.

Charman, W. N., Atchison, D. A. & Scott, D. H. 2002. Theoretical analysis of peripheral imaging after excimer laser corneal refractive surgery for myopia. *Journal of Cataract and Refractive Surgery,* 28(11)**,** 2017-2025.

Charman, W. N. & Saunders, B. 1990. Theoretical and practical factors influencingthe optical performance of contact lenses for the presbyope. *Journal of the British Contact Lens Association,* 13**,** 67-75.

Chen, H.-B., Yamabayashi, S., Ou, B., Tanaka, Y., Ohno, S. & Tsukahara, S. 1998. Histochemical study on rat tear film and ocular surface epithelial cells. *Current Eye Research,* 17(6)**,** 642-649.

Chen, S., Png, E. & Tong, L. 2009. Comparison of two artificial tear formulations using aberrometry. *Clinical and Experimental Optometry,* 92(6)**,** 519-519.

Cheng, X., Bradley, A., Hong, X. & Thibos, L. N. 2003. Relationship between refractive error and monochromatic aberrations of the eye. *Optometry & Vision Science,* 80(1)**,** 43-49.

Cheng, Z.-Y., He, J. C., Zhou, X.-T. & Chu, R. Y. 2008. Effect of flap thickness on higher order wavefront aberrations induced by LASIK: a bilateral study. *Journal of Refractive Surgery,* 24(5)**,** 524-529.

Cheung, N. & Wong, T. Y. 2007. Obesity and eye diseases. *Survey of Ophthalmology,* 52(2)**,** 180-195.

Chia, E. M., Mitchell, P., Rochtchina, E., Lee, A. J., Maroun, R. & Wang, J. J. 2003. Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. *Clinical & Experimental Ophthalmology,* 31(3)**,** 229-232.

Cho, P., & Boost, M. V. (2013). Daily disposable lenses: the better alternative. *Contact Lens & Anterior Eye*, *36*(1), 4-12.

Choi, M., Weiss, S., Schaeffel, F., Seidemann, A., Howland, H. C., Wilhelm, B. & Wilhelm, H. 2000. Laboratory, clinical, and kindergarten test of a new eccentric infrared photorefractor (PowerRefractor). *Optometry & Vision Science,* 77(10)**,** 537-548.

Choong, Y.-F., Chen, A.-H. & Goh, P.-P. 2006. A comparison of autorefraction and subjective refraction with and without cycloplegia in primary school children. *American Journal of Ophthalmology,* 142(1)**,** 68-74.

Chylack Jr, L. T., Leske, M. C., McCarthy, D., Khu, P., Kashiwagi, T. & Sperduto, R. 1989. Lens opacities classification system II (LOCS II). *Archives of Ophthalmology,* 107(7)**,** 991-997.

Chylack Jr, L. T., Leske, M. C., Sperduto, R., Khu, P. & McCarthy, D. 1988. Lens opacities classification system. *Archives of Ophthalmology,* 106(3)**,** 330-334.

Chylack, L. T., Wolfe, J. K., Singer, D. M., Leske, M. C., Bullimore, M. A., Bailey, I. L., Friend, J., McCarthy, D. & Wu, S. Y. 1993. The lens opacities classification system III.The Longitudinal Study of Cataract Study Group. *Archives of Ophthalmology,* 111(6), 831-836.

Cillino, S., Casuccio, A., Di Pace, F., Morreale, R., Pillitteri, F., Cillino, G. & Lodato, G. 2008. One-year outcomes with new-generation multifocal intraocular lenses. *Ophthalmology,* 115(9)**,** 1508-1516.

Cionni, R., Chang, D., Donnenfeld, E., Lane, S., McCulley, J. & Solomon, K. 2009. Clinical outcomes and functional visual performance: comparison of the ReSTOR apodised diffractive intraocular lens to a monofocal control. *British Journal of Ophthalmology,* 93(9)**,** 1215-1219.

Clare, G., Pitts, J. A., Edgington, K. & Allan, B. D. 2010. From beach lifeguard to astronaut: occupational vision standards and the implications of refractive surgery. *British Journal of Ophthalmology,* 94(4)**,** 400-405.

Cleary, G., Spalton, D., Patel, P., Lin, P. F. & Marshall, J. 2009. Diagnostic accuracy and variability of autorefraction by the Tracey Visual Function Analyzer and the Shin-Nippon NVision-K 5001 in relation to subjective refraction. *Ophthalmic and Physiological Optics,* 29(2)**,** 173-181.

Cohen, A. L. 1993. Diffractive bifocal lens designs. *Optometry & Vision Science,* 70(6)**,** 461-468.

Cohen, J. (1992). A power primer. *Psychological bulletin*, *112*(1), 155.

Cohen, D., Neil, H., Sparrow, J., Thorogood, M. & Mann, J. 1990. Lens opacity and mortality in diabetes. *Diabetic Medicine,* 7(7)**,** 615-617.

Craig, J. P., Purslow, C., Murphy, P. J. & Wolffsohn, J. S. W. 2010. Effect of a liposomal spray on the pre-ocular tear film. *Contact Lens and Anterior Eye,* 33(2)**,** 83-87.

Cubbidge, R. 2006. Eye Essentials: Visual Fields.Doshi S.,Harvey, W.(eds.)*,* UK:Butterworth-Heinemann.

Dair, G. T., Ashman, R. A., Eikelboom, R. H., Reinholz, F. & van Saarloos, P. P. 2001. Absorption of 193-and 213-nm laser wavelengths in sodium chloride solution and balanced salt solution. *Archives of Ophthalmology,* 119(4)**,** 533-557.

Daniels, J. T., Dart, J. K., Tuft, S. J. & Khaw, P. T. 2001. Corneal stem cells in review. *Wound repair and regeneration,* 9(6)**,** 483-494.

Dastjerdi, M. H. & Soong, H. K. 2002. LASEK (laser subepithelial keratomileusis). *Current Opinion in Ophthalmology,* 13(4)**,** 261-263.

Davies, L. N., Mallen, E. A. H. & Wolffsohn, J. S. 2003a. Clinical evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR-5100K autorefractor. *Optometry & Vision Science,* 80(4)**,** 320-324.

Davies, N., Diaz-Santana, L. & Lara-Saucedo, D. 2003b. Repeatability of ocular wavefront measurement. *Optometry & Vision Science,* 80(2)**,** 142-150.

de Jong, P. T. 2013. Cataract, Age-Related Macular Degeneration, and Primary Open-Angle Glaucoma: Risk Factors *In:* Scholl, H., Massof, R. & West, S. (eds.) *Ophthalmology and the Ageing Society.* Heidelberg: Springer, 33.

de Vries, N. E., Webers, C. A. B., Montés-Micó, R., Ferrer-Blasco, T. & Nuijts, R. M. M. A. 2010. Visual outcomes after cataract surgery with implantation of a+ 3.00 D or+ 4.00 D aspheric diffractive multifocal intraocular lens: Comparative study. *Journal of Cataract and Refractive Surgery,* 36**,** 1316-1322.

Dexl, A. K., Zaluski, S., Rasp, M. & Grabner, G. 2013. Visual performance after bilateral implantation of a new diffractive aspheric multifocal intraocular lens with a 3.5 D addition. *European Journal of Ophthalmology,* doi: 10.5301/ejo.5000315. [Epub ahead of print]

Dick, H. B., Aliyeva, S. & Tehrani, M. 2005. Change in pupil size after implantation of an iris-fixated toric phakic intraocular lens. *Journal of Cataract and Refractive Surgery,* 31(2)**,** 302-307.

Dietze, H. H. & Cox, M. J. 2003. On-and off-eye spherical aberration of soft contact lenses and consequent changes of effective lens power. *Optometry & Vision Science,* 80(2)**,** 126-134.

Dooley, I., D'Arcy, F. & O'Keefe, M. 2012. Comparison of dry-eye disease severity after laser in situ keratomileusis and laser-assisted subepithelial keratectomy. *Journal of Cataract & Refractive Surgery,* 38(6)**,** 1058-1064.

Dougherty, P. J., Wellish, K. L. & Maloney, R. K. 1994. Excimer laser ablation rate and corneal hydration. *American journal of ophthalmology,* 118(2)**,** 169-176.

Doughty, M. J. & Glavin, S. 2009. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic and Physiological Optics,* 29(6)**,** 573-583.

Doughty, M. J. & Zaman, M. L. 2000. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Survey of Ophthalmology,* 44(5)**,** 367-408.

Dua, H., Gomes, J. & Singh, A. 1994. Corneal epithelial wound healing. *The British Journal of Ophthalmology,* 78(5)**,** 401-408.

Dua, H. S., Faraj, L. A., Said, D. G., Gray, T. & Lowe, J. 2013. Human Corneal Anatomy Redefined: A Novel Pre-Descemet's Layer (Dua's Layer). *Ophthalmology*, S0161-6420.

Dupps Jr, W. J., Kohnen, T., Mamalis, F. N., Rosen, E. S., Koch, D. D., Obstbaum, S. A. & Stulting, R. D. 2011. Standardized graphs and terms for refractive surgery results. *Journal of Refractive Surgery,* 27(1)**,** 7-9.

Edelhauser, H., Van Horn, D., Schultz, R. & Hyndiuk, R. 1976. Comparative toxicity of intraocular irrigating solutions on the corneal endothelium. *American Journal of Ophthalmology,* 81(4)**,** 473-481.

Edelhauser, H. F. 2000. The resiliency of the corneal endothelium to refractive and intraocular surgery. *Cornea,* 19(3)**,** 263-273.

Efron, S., Efron, N. & Morgan, P. B. 2008. Repeatability and reliability of ocular aberration measurements in contact lens wear. *Contact Lens and Anterior Eye,* 31(2)**,** 81-88.

Elliott, D., Bullimore, M. & Bailey, I. 1991. Improving the reliability of the Pelli-Robson contrast sensitivity test. *Clinical Vision Science* 6**,** 471-475.

Elliott, D. B., Sanderson, K. & Conkey, A. 1990. The reliability of the Pelli-Robson contrast sensitivity chart. *Ophthalmic and Physiological Optics,* 10(1)**,** 21-24.

Erickson, P. 1988. Potential range of clear vision in monovision. *Journal of the American Optometric Association,* 59(3)**,** 203-205.

Espana, E. M., Grueterich, M., Mateo, A., Romano, A. C., Yee, S. B., Yee, R. W. & Tseng, S. C. 2003. Cleavage of corneal basement membrane components by ethanol exposure in laser-assisted subepithelial keratectomy. *Journal of Cataract & Refractive Surgery,* 29(6)**,** 1192-1197.

Farjo, A., McDermott, M. & Soong, H. 2009. Corneal anatomy, physiology, and wound healing. *Ophthalmology, 3rd edn. Edinburgh, Mosby Elsevier: Elsevier Inc***,** 203-8.

Faul, F., Erdfelder, E., Lang, A. G. & Buchner, A. 2007. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods,* 39(2)**,** 175-191.

Ferrer-Blasco, T., García-Lázaro, S., Montés-Micó, R., Cerviño, A. & González-Méijome, J. M. 2010. Dynamic changes in the air–tear film interface modulation transfer function. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 248(1)**,** 127-132.

Ferrer-Blasco, T. & Madrid-Costa, D. 2010. Stereoacuity with simultaneous vision multifocal contact lenses. *Optometry & Vision Science,* 87(9)**,** E663-E668.

Ficker, L., Bates, A., Steele, A. D. M. G., Lyons, C., Milliken, A., Astin, C., Slattery, K. & Kirkness, C. 1993. Excimer laser photorefractive keratectomy for myopia: 12 month follow-up. *Eye,* 7(Pt 5)**,** 617-624.

Fincham, E. F. 1951. The accommodation reflex and its stimulus. *The British Journal of Ophthalmology*, *35*(7), 381.

Fini, M. E. 1999. Keratocyte and fibroblast phenotypes in the repairing cornea. *Progress in retinal and eye research,* 18(4)**,** 529-551.

Foster, A. & Johnson, G. J. 1990. Magnitude and causes of blindness in the developing world. *International Ophthalmology,* 14(3)**,** 135-140.

Foulks, G. N. 2003. Challenges and pitfalls in clinical trials of treatments for dry eye. *The Ocular Surface,* 1(1)**,** 20-30.

Foulks, G. N. & Borchman, D. 2010. Meibomian Gland Dysfunction: The Past, Present, and Future. *Eye & Contact Lens,* 36(5)**,** 249-253.

French, C., Jennings JAM. 1974. Errors in subjective refraction:an exploratory study. *Ophthalmic and Physiological Optics,* 14, 797-806.

Fujishima, H., Toda, I., Shimazaki, J. & Tsubota, K. 1996. Allergic conjunctivitis and dry eye. *British Journal of Ophthalmology,* 80(11)**,** 994.

Galvis, V., Tello, A., Guerra, A. R., Rey, J. J. & Camacho, P. A. 2013. Risk factors and visual results in cases of LASIK flap repositioning due to folds or dislocation: case series and literature review. *International Ophthalmology***,** 1-8.

Gartry, D. S., Muir, M., Lohmann, C. P. & Marshall, J. 1992. The effect of topical corticosteroids on refractive outcome and corneal haze after photorefractive keratectomy. A prospective, randomized, double-blind trial. *Archives of Ophthalmology,* 110(7)**,** 944.

Geroski, D. H., Matsuda, M., Yee, R. W. & Edelhauser, H. F. 1985. Pump function of the human corneal endothelium. *Ophthalmology,* 92(6)**,** 759-763.

Gifford, P., Cannon, T., Lee, C., Lee, D., Lee, H. F. & Swarbrick, H. A. 2013. Ocular aberrations and visual function with multifocal versus single vision soft contact lenses. *Contact Lens and Anterior Eye*, 36(2),66-73.

Gillespie, B. W., Musch, D. C., Guire, K. E., Mills, R. P., Lichter, P. R., Janz, N. K. & Wren, P. A. 2003. The collaborative initial glaucoma treatment study: baseline visual field and test–retest variability. *Investigative Ophthalmology & Visual Science,* 44(6)**,** 2613-2620.

Ginsburg, A. P. 1978. Visual Information Processing Based on Spatial Filters Constrained by Biological Data. U.S. Air Force Aerospace Medical Research Laboratory: Wright-Patterson AFB, OH, 1978; Vols. 1 and 2.

Gispets, J., Arjona, M., Pujol, J., Vilaseca, M. & Cardona, G. 2011. Task oriented visual satisfaction and wearing success with two different simultaneous vision multifocal soft contact lenses. *Journal of Optometry,* 4**,** 76-84.

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

Gogate, P., Deshpande, M. & Wormald, R. 2003. Is manual small incision cataract surgery affordable in the developing countries? A cost comparison with extracapsular cataract extraction. *British Journal of Ophthalmology,* 87(6)**,** 843-846.

Goss, D. A. & Grosvenor, T. 1996. Reliability of refraction: a literature review. *Journal of the American Optometric Association,* 67(10)**,** 619-630.

Goto, E., Yagi, Y., Matsumoto, Y. & Tsubota, K. 2002. Impaired functional visual acuity of dry eye patients. *American Journal of Ophthalmology,* 133(2)**,** 181-186.

Guirao, A., Redondo, M., Geraghty, E., Piers, P., Norrby, S. & Artal, P. 2002. Corneal optical aberrations and retinal image quality in patients in whom monofocal intraocular lenses were implanted. *Archives of Ophthalmology,* 120(9)**,** 1143-1151.

Guirao, A., Williams, D. R., & Cox, I. G. (2001). Effect of rotation and translation on the expected benefit of an ideal method to correct the eye's higher-order aberrations. *JOSA A*, *18*(5), 1003-1015.

Gupta, N. & Naroo, S. A. 2006. Factors influencing patient choice of refractive surgery or contact lenses and choice of centre. *Contact Lens and Anterior Eye,* 29(1)**,** 17-23.

Gupta, N., Naroo, S. A. & Wolffsohn, J. S. 2009. Visual comparison of multifocal contact lens to monovision. *Optometry & Vision Science,* 86(2)**,** E98-E105.

Haegerstrom-Portnoy, G., Schneck, M. E., Lott, L. A. & Brabyn, J. A. 2000. The relation between visual acuity and other spatial vision measures. *Optometry & Vision Science,* 77(12)**,** 653-662.

Han, J., Han, K. E., Ahn, J. M., Jeong, S. H., Lee, H. K., Seo, K. Y., Kim, E. K. & Kim, T. I. 2012. Influence of Pupil Size on Visual Acuity after Implantation of the TECNIS 1-Piece Intraocular Lens. *Journal of the Korean Ophthalmological Society,* 53(11)**,** 1615-1620.

Hawkins, A. S., Szlyk, J. P., Ardickas, Z., Alexander, K. R. & Wilensky, J. T. 2003. Comparison of contrast sensitivity, visual acuity, and Humphrey visual field testing in patients with glaucoma. *Journal of Glaucoma,* 12(2)**,** 134-138.

Hay, E. M., Thomas, E., Pal, B., Hajeer, A., Chambers, H. & Silman, A. 1998. Weak association between subjective symptoms of and objective testing for dry eyes and dry mouth: results from a population based study. *British Medical Journal,* 57(1)**,** 20-24.

Hazel, C. A., Cox, M. J. & Strang, N. C. 2003. Wavefront aberration and its relationship to the accommodative stimulus-response function in myopic subjects. *Optometry & Vision Science,* 80(2)**,** 151-158.

He, J. C., Marcos, S., Webb, R. & Burns, S. A. 1998. Measurement of the wave-front aberration of the eye by a fast psychophysical procedure. *Journal of the Optical Society of America A, Optics and Image Science ,* 15(9)**,** 2449-2456.

Heijl, A. Year. Reliability parameters in computerized perimetry. *In:* Seventh International Visual Field Symposium, Amsterdam, September 1987. Springer, 593-600.

Heijl, A., Lindgren, G. & Olsson, J. 1987. Normal variability of static perimetric threshold values across the central visual field. *Archives of Ophthalmology,* 105(11)**,** 1544-1549.

Heijl, A. & Patella, V. 2002. Essential Perimetry: The Field Analyzer Primer, 3rd ed. Dublin, CA: Carl Zeiss Meditec. Inc.

Herreras, J., Pastor, J., Calonge, M. & Asensio, V. 1992. Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology,* 99(7)**,** 1082-1088.

Hickenbotham, A., Roorda, A., Steinmaus, C. & Glasser, A. 2012. Meta-Analysis of Sex Differences in Presbyopia. *Investigative Ophthalmology & Visual Science,* 53(6)**,** 3215-3220.

Himebaugh, N. L., Begley, C. G., Bradley, A. & Wilkinson, J. A. 2009. Blinking and tear break-up during four visual tasks. *Optometry & Vision Science,* 86(2)**,** E106-14.

Himebaugh, N. L., Nam, J., Bradley, A., Liu, H., Thibos, L. N. & Begley, C. G. 2012. Scale and Spatial Distribution of Aberrations Associated with Tear Breakup. *Optometry & Vision Science,* 89(11)**,** 1590-1600.

Ho, A. (2003). Aberration correction with soft contact lens: Is the postlens tear film important?. *Eye & contact lens*, *29*(1), S182-S185.

Holden, B. A., Fricke, T. R., Ho, S., Wong, R., Schlenther, G., Cronje, S., ... & Frick, K. D. (2008). Global vision impairment due to uncorrected presbyopia. *Archives of Ophthalmology*, *126*(12), 1731.

Hoffman, R. S., Fine, I. H. & Packer, M. 2005. New phacoemulsification technology. *Current Opinion in Ophthalmology,* 16(1)**,** 38-43.

Hohberger, B., Laemmer, R., Adler, W., Juenemann, A. G. & Horn, F. K. 2007. Measuring contrast sensitivity in normal subjects with OPTEC® 6500: influence of age

and glare. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 245(12)**,** 1805-1814.

Holden, B. A., Fricke, T. R., Ho, S., Wong, R., Schlenther, G., Cronje, S., Burnett, A., Papas, E., Naidoo, K. S. & Frick, K. D. 2008. Global vision impairment due to uncorrected presbyopia. *Archives of Ophthalmology,* 126(12)**,** 1731-1739.

Holladay, J. T. 1997. Proper method for calculating average visual acuity. *Journal of Refractive Surgery,* 13(4)**,** 388-391.

Holladay, J. T., Piers, P. A., Koranyi, G., van der Mooren, M. & Norrby, N. S. 2002. A new intraocular lens design to reduce spherical aberration of pseudophakic eyes. *Journal of Refractive Surgery,* 18(6)**,** 683-691.

Holman, N., Forouhi, N., Goyder, E. & Wild, S. 2011. The Association of Public Health Observatories (APHO) diabetes prevalence model: estimates of total diabetes prevalence for England, 2010–2030. *Diabetic Medicine,* 28(5)**,** 575-582.

Holt, D. G., Sikder, S. & Mifflin, M. D. 2012. Surgical management of traumatic LASIK flap dislocation with macrostriae and epithelial ingrowth 14 years postoperatively. *Journal of Cataract & Refractive Surgery,* 38(2)**,** 357-361.

Hong, X., Himebaugh, N. & Thibos, L. N. 2001. On-eye evaluation of optical performance of rigid and soft contact lenses. *Optometry & Vision Science,* 78(12)**,** 872-880.

Hood, C. T., Krueger, R. R. & Wilson, S. E. 2013. The association between femtosecond laser flap parameters and ocular aberrations after uncomplicated custom myopic LASIK. *Graefe's Archive for Clinical and Experimental Ophthalmology***,** 1-8.

Howland, H. C. & Howland, B. 1977. A subjective method for the measurement of monochromatic aberrations of the eye. *Journal of the Optical Society of America,* 67(11)**,** 1508-1518.

Huang, F.-C., Tseng, S.-H., Shih, M.-H. & Chen, F. K. 2002. Effect of artificial tears on corneal surface regularity, contrast sensitivity, and glare disability in dry eyes. *Ophthalmology,* 109(10)**,** 1934-1940.

Hudson, C., Wild, J. M. & O'Neill, E. C. 1994. Fatigue effects during a single session of automated static threshold perimetry. *Investigative Ophthalmology and Visual Science,* 35(5)**,** 268-280.

Hunkeler, J. D., Coffman, T. M., Paugh, J., Lang, A., Smith, P., & Tarantino, N. (2002). Characterization of visual phenomena with the Array multifocal intraocular lens. *Journal of Cataract & Refractive Surgery*, *28*(7), 1195-1204.

Hütz, W. W., Eckhardt, H. B., Röhrig, B. & Grolmus, R. 2006. Reading ability with 3 multifocal intraocular lens models. *Journal of Cataract and Refractive Surgery,* 32(12)**,** 2015-2021.

Iglesias, I., Berrio, E, Artal, P. 1998. Estimates of the ocular wave aberration from pairs of double-pass retinal images. *Journal of the Optical Society of America, Optics and Image Science,* 15(9)**,** 2466-2476.

Iglesias, I., Ragazzoni, R, Julien, Y, Artal, P. 2002. Extended source pyramid wave-front sensor for the human eye. *Optics Express,* 10**,** 419-428.

Inoue, M., Bissen-Miyajima, H., Yoshino, M. & Suzuki, T. 2009. Wavy horizontal artifacts on optical coherence tomography line-scanning images caused by diffractive multifocal intraocular lenses. *Journal of Cataract & Refractive Surgery,* 35(7)**,** 1239-1243.

Inoue, M., Noda, T., Mihashi, T., Ohnuma, K., Bissen-Miyajima, H. & Hirakata, A. 2011. Quality of image of grating target placed in model of human eye with corneal aberrations as observed through multifocal intraocular lenses. *American Journal of Ophthalmology,* 151(4)**,** 644-652.

Ishibashi, T., Yokoi, N. & Kinoshita, S. 2003. Comparison of the short-term effects on the human corneal surface of topical timolol maleate with and without benzalkonium chloride. *Journal of Glaucoma,* 12(6)**,** 486-490.

Iskander, D. R., Collins, M. J., Davis, B. & Carney, L. G. 2000. Monochromatic aberrations and characteristics of retinal image quality. *Clinical and Experimental Optometry,* 83(6)**,** 315-322.

Jaffe, N. S., Jaffe, M. S. & Jaffe, G. F. 1990. *Cataract Surgery and its Complications,* 5th ed. St. Louis, CV Mosby.

Jester, J. V., Moller-Pedersen, T., Huang, J., Sax, C. M., Kays, W. T., Cavangh, H. D., Petroll, W. M. & Piatigorsky, J. 1999. The cellular basis of corneal transparency: evidence for 'corneal crystallins'. *Journal of Cell Science,* 112(Pt 5)**,** 613-622.

Jinabhai, A., O'Donnell, C. & Radhakrishnan, H. 2010. A comparison between subjective refraction and aberrometry-derived refraction in keratoconus patients and control subjects. *Current Eye Research,* 35(8)**,** 703-714.

Johnson, M. E. 2009. The association between symptoms of discomfort and signs in dry eye. *The Ocular Surface,* 7(4)**,** 199-211.

Jong, C., Stolwijk, T., Kuppens, E., Keizer, R. & Best, J. 1994. Topical timolol with and without benzalkonium chloride: epithelial permeability and autofluorescence of the cornea in glaucoma. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 232(4)**,** 221-224.

Jorge, J., González-Méijome, J. M., Queirós, A., Fernandes, P. & Diaz-Rey, J. A. 2011. A comparison of the NCT Reichert R7 with Goldmann applanation tonometry and the Reichert ocular response analyzer. *Ophthalmic and Physiological Optics,* 31(2)**,** 174-179.

Kawamura, R., Inoue, I., Shinoda, K. & Bissen-Miyajima, H. 2008. Intraoperative findings during vitreous surgery after implantation of diffractive multifocal intraocular lens. *Journal of Cataract and Refractive Surgery,* 34(6)**,** 1048-1049.

Kaya, V., Oncel, B., Sivrikaya, H. & Yilmaz, O. F. 2004. Prospective, paired comparison of laser in situ keratomileusis and laser epithelial keratomileusis for myopia less than-6.00 diopters. *Journal of Refractive Surgery,* 20(3)**,** 223-228.

Kermani, O. & Lubatschowski, H. 1991. Structure and dynamics of photo-acoustic shock-waves in 193 nm excimer laser photo-ablation of the cornea]. *Fortschritte der Ophthalmologie: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft,* 88(6)**,** 748-753.

Khor, W. B. & Afshari, N. A. 2013. The role of presbyopia-correcting intraocular lenses after laser in situ keratomileusis. *Current Opinion in Ophthalmology,* 24(1)**,** 35-40.

Khoramnia, R., Auffarth, G. U., Rabsilber, T. M. & Holzer, M. P. 2012. Implantation of a multifocal toric intraocular lens with a surface-embedded near segment after repeated LASIK treatments. *Journal of Cataract & Refractive Surgery,* 38(11)**,** 2049-2052.

Kim, T. W., Wee, W. R., Lee, J. H. & Kim, M. K. 2007. Contrast sensitivity after LASIK, LASEK, and wavefront-guided LASEK with the VISX S4 laser. *Journal of Refractive Surgery,* 23(4)**,** 355-361.

Kinge, B., Midelfart, A. & Jacobsen, G. 1996. Clinical evaluation of the Allergan Humphrey 500 autorefractor and the Nidek AR-1000 autorefractor. *British Journal of Ophthalmology,* 80(1)**,** 35-39.

Kirwan, C. & O'Keefe, M. 2009. Comparative study of higher-order aberrations after conventional laser in situ keratomileusis and laser epithelial keratomileusis for myopia using the technolas 217z laser platform. *American Journal of Ophthalmology,* 147(1)**,** 77-83.

Klyce, S. D., Karon, M. D. & Smolek, M. K. 2004. Advantages and disadvantages of the Zernike expansion for representing wave aberration of the normal and aberrated eye. *Journal of Refractive Surgery,* 20(5)**,** 537-541.

Koh, S., Maeda, N., Hirohara, Y., Mihashi, T., Bessho, K., Hori, Y., Inoue, T., Watanabe, H., Fujikado, T. & Tano, Y. 2008a. Serial measurements of higher-order aberrations after blinking in patients with dry eye. *Investigative Ophthalmology & Visual Science,* 49(1)**,** 133-138.

Koh, S., Maeda, N., Hirohara, Y., Mihashi, T., Ninomiya, S., Bessho, K., Watanabe, H., Fujikado, T. & Tano, Y. 2006a. Serial measurements of higher-order aberrations after blinking in normal subjects. *Investigative Ophthalmology & Visual Science,* 47(8)**,** 3318-3324.

Koh, S., Maeda, N., Hori, Y., Inoue, T., Watanabe, H., Hirohara, Y., Mihashi, T., Fujikado, T. & Tano, Y. 2008b. Effects of suppression of blinking on quality of vision in borderline cases of evaporative dry eye. *Cornea,* 27(3)**,** 275-278.

Koh, S., Maeda, N., Ninomiya, S., Watanabe, H., Fujikado, T., Tano, Y., Hirohara, Y. & Mihashi, T. 2006b. Paradoxical increase of visual impairment with punctal occlusion in a patient with mild dry eye. *Journal of Cataract & Refractive Surgery,* 32(4)**,** 689-691.

Kohnen, T., Klaproth, O. K. & Bühren, J. 2009. Effect of intraocular lens asphericity on quality of vision after cataract removal: an intraindividual comparison. *Ophthalmology,* 116(9)**,** 1697-1706.

Koller, G., Haas, A., Zulauf, M., Koerner, F. & Mojon, D. 2001. Influence of refractive correction on peripheral visual field in static perimetry. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 239(10)**,** 759-762.

Koretz, J. F., Strenk, S. A., Strenk, L. M. & Semmlow, J. L. 2004. Scheimpflug and high-resolution magnetic resonance imaging of the anterior segment: a comparative study. *Journal of the Optical Society of America A, Optics image science and vision,* 21(3)**,** 346-354.

Krueger, R. R., Seiler, T., Gruchman, T., Mrochen, M. & Berlin, M. S. 2001. Stress wave amplitudes during laser surgery of the cornea. *Ophthalmology,* 108(6)**,** 1070-1074.

Kudrna, G. R., Stanley, M. A. & Remington, L. A. 1995. Pupillary dilation and its effects on automated perimetry results. *Journal of the American Optometric Association,* 66(11)**,** 675-680.

Kulkarni, S. V., AlMahmoud, T., Priest, D., Taylor, S. E., Mintsioulis, G. & Jackson, W. B. 2013. Long-Term Visual and Refractive Outcomes following Surface Ablation Techniques in a Large Population for Myopia Correction. *Investigative Ophthalmology & Visual Science,* 54(1)**,** 609-619.

Kutzko, K. E., Brito, C. F. & Wall, M. 2000. Effect of instructions on conventional automated perimetry. *Investigative Ophthalmology and Visual Science,* 41(7)**,** 2006-2013.

Lackner, B., Pieh, S., Schmidinger, G., Hanselmayer, G., Simader, C., Reitner, A. & Skorpik, C. 2003. Glare and halo phenomena after laser in situ keratomileusis. *Journal of Cataract and Refractive Surgery,* 29(3)**,** 444-450.

Lackner, B., Schmidinger, G., Pieh, S., Funovics, M. A. & Skorpik, C. 2005. Repeatability and reproducibility of central corneal thickness measurement with Pentacam, Orbscan, and ultrasound. *Optometry and Vision Science,* 82(10)**,** 892-899.

Lane, S. S., Morris, M., Nordan, L., Packer, M., Tarantino, N. & Wallace R.B.3rd. 2006. Multifocal intraocular lenses. *Ophthalmology Clinics of North America,* 19(1)**,** 89-105.

Lapid-Gortzak, R., van der Linden, J. W., van der Meulen, I., Nieuwendaal, C. & van den Berg, T. 2010. Straylight measurements in laser in situ keratomileusis and laser-assisted subepithelial keratectomy for myopia. *Journal of Cataract & Refractive Surgery,* 36(3)**,** 465-471.

Laretzaki, G., Plainis, S., Vrettos, I., Chrisoulakis, A., Pallikaris, I. & Bitsios, P. 2011. Threat and trait anxiety affect stability of gaze fixation. *Biological Psychology,* 86(3)**,** 330-336.

Lee, E. K., Kwon, J.-W., Hyon, J. Y. & Han, Y. K. 2012. Satisfaction Level of Physicians Who Have Undergone Corneal Refractive Surgery. *Korean Journal of Ophthalmology,* 26(5)**,** 331-338.

Lee, J. B., Choe, C.-M., Kim, H. S., Seo, K. Y., Seong, G. J. & Kim, E. K. 2002. Comparison of TGF-beta1 in tears following laser subepithelial keratomileusis and photorefractive keratectomy. *Journal of Refractive Surgery,* 18(2)**,** 130-134.

Lee, J. B., Seong, G. J., Lee, J. H., Seo, K. Y., Lee, Y. G. & Kim, E. K. 2001. Comparison of laser epithelial keratomileusis and photorefractive keratectomy for low to moderate myopia. *Journal of Cataract & Refractive Surgery,* 27(4)**,** 565-570.

Legge, G. E., Mullen, K. T., Woo, G. C. & Campbell, F. 1987. Tolerance to visual defocus. *Journal of the Optical Society of America,* 4(5)**,** 851-863.

Lembares, A., Hu, X.-H. & Kalmus, G. W. 1997. Absorption spectra of corneas in the far ultraviolet region. *Investigative Ophthalmology & Visual Science,* 38(6)**,** 1283-1287.

Lemp, M. A. 2007. The definition and classification of dry eye disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *The Ocular Surface,* 5(2)**,** 75-92.

Lemp, M. A. & Hamill Jr, J. R. 1973. Factors affecting tear film breakup in normal eyes. *Archives of Ophthalmology,* 89(2)**,** 103-105.

Lewis, R., Johnson, C., Keltner, J. & Labermeier, P. 1986. Variability of quantitative automated perimetry in normal observers. *Ophthalmology,* 93(7)**,** 878-881.

Li, K. Y. & Yoon, G. 2006. Changes in aberrations and retinal image quality due to tear film dynamics. *Optics Express,* 14(25)**,** 12552-12559.

Li, S. M., Zhan, S. Y., Li, S. Y., Peng, X. X., Hu, J. & Wang, N. L. 2012. Photorefractive keratectomy (PRK) versus laser-assisted subepithelial keratectomy (LASEK) for myopia correction. *The Cochrane Library*.

Liang, J., Grimm, B., Goelz, S. & Bille, J. 1994. Objective measurement of wave aberrations of the human eye with the use of a Hartmann-Shack wave-front sensor. *Journal of the Optical Society of America. A, Optics, image science, and vision,* 11(7)**,** 1949-1957.

Liang, J. & Williams, D. R. 1997. Aberrations and retinal image quality of the normal human eye. *Journal of the Optical Society of America. A, Optics, image science, and vision,* 14(11)**,** 2873-2883.

Limnopoulou, A. N., Bouzoukis, D. I., Kymionis, G. D., Panagopoulou, S. I., Plainis, S., Pallikaris, A. I., ... & Pallikaris, I. G. (2013). Visual outcomes and safety of a refractive corneal inlay for presbyopia using femtosecond laser. *Journal of Refractive Surgery*, *29*(1), 12-18.

Lin, Y., Carrel, H., Wang, I., Lin, P. & Hu, F. Effect of tear film break-up on higher order aberrations of the anterior cornea in normal, dry, and post-LASIK eyes. *Journal of refractive surgery,* 21(5)**,** S525.

Litwak, S., Zadok, D., Garcia-de Quevedo, V., Robledo, N. & Chayet, A. S. 2002. Laser-assisted subepithelial keratectomy versus photorefractive keratectomy for the correction of myopia: a prospective comparative study. *Journal of Cataract & Refractive Surgery,* 28(8)**,** 1330-1333.

Liu, H., Begley, C. G., Chalmers, R., Wilson, G., Srinivas, S. P. & Wilkinson, J. A. 2006. Temporal progression and spatial repeatability of tear breakup. *Optometry & Vision Science,* 83(10)**,** 723-730.

Liu, H., Thibos, L., Begley, C. G. & Bradley, A. 2010. Measurement of the time course of optical quality and visual deterioration during tear break-up. *Investigative Ophthalmology & Visual Science,* 51(6)**,** 3318-3326.

Livingston, P., Guest, C., Stanislavsky, Y., Lee, S., Bayley, S., Walker, C., McKean, C. & Taylor, H. R. 1994. A population-based estimate of cataract prevalence: the Melbourne Visual Impairment Project experience. *Developments in Ophthalmology,* 26**,** 1-6.

Lleó-Pérez, A. & Sanchis Gimeno, J. 2007. Changes in the visual field following laser in situ keratomileusis for myopia. *Ophthalmic and Physiological Optics,* 27(2)**,** 201-209.

Llorente-Guillemot, A., García-Lazaro, S., Ferrer-Blasco, T., Perez-Cambrodi, R. J. & Cerviño, A. 2012. Visual performance with simultaneous vision multifocal contact lenses. *Clinical and Experimental Optometry*, 95(1), 54-59.

Lloyd, I., Goss-Sampson, M., Jeffrey, B., Kriss, A., Russell-Eggitt, I. & Taylor, D. 1992. Neonatal cataract: aetiology, pathogenesis and management. *Eye,* 6(Pt 2)**,** 184-196.

Lohmann, C. P. & Guell, J. L. Year. Regression after LASIK for the treatment of myopia: the role of the corneal epithelium. *Seminars in Ophthalmology*, 1998, 13,(2) 79-82.

Lopes-Ferreira, D., Ribeiro, C., Maia, R., García-Porta, N., Queirós, A., Villa-Collar, C. & González-Méijome, J. M. 2011. Peripheral myopization using a dominant design multifocal contact lens. *Journal of Optometry,* 4**,** 14-21.

López-Gil, Norberto, José Francisco Castejón-Mochón, Antonio Benito, José María Marín, George Lo-a-Foe, Gildas Marin, Bruno Fermigier et al. 2002. Aberration generation by contact lenses with aspheric and asymmetric surfaces. *Journal of Refractive Surgery* 18(5), S603-S609.

Lozato, P., Pisella, P. & Baudouin, C. 2001. The lipid layer of the lacrimal tear film: physiology and pathology. *Journal Francais d'Ophtalmologie,* 24(6)**,** 643-653

Lu, F., Mao, X., Qu, J., Xu, D. & He, J. C. 2003. Monochromatic wavefront aberrations in the human eye with contact lenses. *Optometry & Vision Science,* 80(2)**,** 135-141.

Luo, B. P., Brown, G. C., Luo, S. C. & Brown, M. M. 2008. The quality of life associated with presbyopia. *American Journal of Ophthalmology,* 145(4)**,** 618-622.

Ma, L., Atchison, D. A. & Charman, W. N. 2005. Off-axis refraction and aberrations following conventional laser in situ keratomileusis. *Journal of Cataract and Refractive Surgery,* 31(3)**,** 489-498.

MacRae, S. & Fujieda, M. 2000. Slit skiascopic-guided ablation using the Nidek laser. *Journal of Refractive Surgery,* 16(5)**,** S576-580.

Madrid-Costa, D., Ruiz-Alcocer, J., García-Lázaro, S., Albarrán-Diego, C. & Ferrer-Blasco, T. 2012. Effect of Multizone Refractive Multifocal Contact Lenses on Standard Automated Perimetry. *Eye & Contact Lens,* 38(5)**,** 278-281.

Madrid-Costa, D., García-Lázaro, S., Albarrán-Diego, C., Ferrer-Blasco, T. & Montés-Micó, R. 2013. Visual performance of two simultaneous vision multifocal contact lenses. *Ophthalmic and Physiological Optics,* 33(1)**,** 51-56.

Mallen, E., Wolffsohn, J., Gilmartin, B. & Tsujimura, S. 2001. Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic and Physiological Optics,* 21(2)**,** 101-107.

Marsich, M. M. & Bullimore, M. A. 2000. The repeatability of corneal thickness measures. *Cornea,* 19(6)**,** 792-795.

Martin, J. A. & Roorda, A. 2003. Predicting and assessing visual performance with multizone bifocal contact lenses. *Optometry & Vision Science,* 80(12)**,** 812-819.

McAlinden, C., Skiadaresi, E. & Moore, J. E. 2011. Visual and refractive outcomes following myopic laser-assisted subepithelial keratectomy with a flying-spot excimer laser. *Journal of Cataract & Refractive Surgery,* 37(5)**,** 901-906.

McCarty, D. J. & McCarty, C. A. 2000. Survey of dry eye symptoms in Australian pilots. *Clinical & Experimental Ophthalmology,* 28(3)**,** 169-171.

McCarty, T. M., Hardten, D. R., Anderson, N. J., Rosheim, K. & Samuelson, T. W. 2003. Evaluation of neuroprotective qualities of brimonidine during LASIK. *Ophthalmology,* 110(8)**,** 1615-1625.

McCulley, J. & Shine, W. 1997. A compositional based model for the tear film lipid layer. *Transactions of the American Ophthalmological Society,* 95**,** 79-88.

McGinnigle, S., Naroo, S. A. & Eperjesi, F. 2012. Evaluation of dry eye. *Survey of Ophthalmology,* 57(4)**,** 293-316.

McMonnies, C. W. 2007. Incomplete blinking: exposure keratopathy, lid wiper epitheliopathy, dry eye, refractive surgery, and dry contact lenses. *Contact Lens and Anterior Eye,* 30(1)**,** 37-51.

Miglior, S., Albe, E., Guareschi, M., Mandelli, G., Gomarasca, S. & Orzalesi, N. 2004. Intraobserver and interobserver reproducibility in the evaluation of ultrasonic pachymetry measurements of central corneal thickness. *British Journal of Ophthalmology,* 88(2)**,** 174-177.

Miljanovic, B., Dana, R., Sullivan, D. A. & Schaumberg, D. A. 2007. Impact of dry eye syndrome on vision-related quality of life. *American Journal of Ophthalmology,* 143(3)**,** 409-415.

Miller, D. T., Williams, D. R., Morris, G. M. & Liang, J. 1996. Images of cone photoreceptors in the living human eye. *Vision Research,* 36(8)**,** 1067-1079.

Minassian, D. C., Reidy, A., Lightstone, A. & Desai, P. 2011. Modelling the prevalence of age-related macular degeneration (2010–2020) in the UK: expected impact of anti-vascular endothelial growth factor (VEGF) therapy. *British Journal of Ophthalmology,* 95(10)**,** 1433-1436.

Mirshahi, A., Wesemann, W., Bühren, J. & Kohnen, T. 2010. Factors influencing the reliability of autorefractometry after LASIK for myopia and myopic astigmatism. *American Journal of Ophthalmology,* 150(6)**,** 774-779.

Mitchell, P., Cumming, R. G., Attebo, K. & Panchapakesan, J. 1997. Prevalence of cataract in Australia: the Blue Mountains eye study. *Ophthalmology,* 104(4)**,** 581-588.

Mitchell, P., Hourihan, F., Sandbach, J. & Jin Wang, J. 1999. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology,* 106(10)**,** 2010-2015.

Mohan, R. R., Hutcheon, A. E., Choi, R., Hong, J., Lee, J., Mohan, R. R., Ambrósio, R., Zieske, J. D. & Wilson, S. E. 2003. Apoptosis, necrosis, proliferation, and myofibroblast generation in the stroma following LASIK and PRK. *Experimental Eye Research,* 76(1)**,** 71-87.

Montés-Micó, R. 2008. Comparison of higher order aberrations measured by NIDEK OPD-Scan dynamic skiascopy and Zeiss WASCA Hartmann-Shack aberrometers. *Journal of Refractive Surgery*, *24*.

Montés-Micó, R. 2007. Role of the tear film in the optical quality of the human eye. *Journal of Cataract & Refractive Surgery,* 33(9)**,** 1631-1635.

Montés-Micó, R., Alió, J. L. & Charman, W. N. 2005. Postblink changes in the ocular modulation transfer function measured by a double-pass method. *Investigative Ophthalmology & Visual Science,* 46(12)**,** 4468-4473.

Montés-Micó, R., Caliz, A. & Alio, J. L. 2004a. Changes in ocular aberrations after instillation of artificial tears in dry-eye patients. *Journal of Cataract and Refractive Surgery,* 30(8)**,** 1649-1652.

Montés-Micó, R., Caliz, A. & Alio, J. L. 2004b. Wavefront analysis of higher order aberrations in dry eye patients. *Journal of Refractive Surgery***,** 20(3), 243-247.

Montés-Micó, R. & Charman, W. N. 2002. Image quality and visual performance in the peripheral visual field following photorefractive keratectomy. *Journal of Refractive Surgery,* 18(1)**,** 14-22.

Montolio, F. G. J., Wesselink, C., Gordijn, M. & Jansonius, N. M. 2012. Factors that influence standard automated perimetry test results in glaucoma: test reliability, technician experience, time of day, and season. *Investigative Ophthalmology & Visual Science,* 53(11)**,** 7010-7017.

Moreno-Barriuso, E., Lloves, J. M., Marcos, S., Navarro, R., Llorente, L. & Barbero, S. 2001. Ocular aberrations before and after myopic corneal refractive surgery: LASIK-induced changes measured with laser ray tracing. *Investigative ophthalmology & visual science,* 42(6)**,** 1396-1403.

Morgan, P. B., Efron, N. & Woods, C. A. 2011. An international survey of contact lens prescribing for presbyopia. *Clinical and Experimental Optometry,* 94(1)**,** 87-92.

Morgan, P. B. & Maldonado-Codina, C. 2009. Corneal staining: Do we really understand what we are seeing? *Contact Lens and Anterior Eye,* 32(2)**,** 48-54.

Morgan, P. B., Woods, C. A., Tranoudis, I. G., Helland, M., Efron, N., Orihuela, G.C., Grupcheva, C. N., Jones, D., Tan, K.-O., Pesinova, A., Ravn, O., Santodomingo, J.,Malet, F.,Sze, L., Cheng, P. Végh, M., Erdinest, N., Ragnarsdóttir, J.B., Montani, G., Sun Chu, B., Bendoriene , J., van der Worp, E., Awasthi, S., Lam, W., Casablanca, J., González-Méijome, J.M., Johansson, O., Stabuc Silih, M., Hsiao, J. & Nichols, J.J. 2013. International contact lens prescribing in 2012. *Contact Lens Spectrum,* (available at http://www.clspectrum.com/articleviewer.aspx?articleID=107854, accessed 29/04/2013).

Mostafaei, A., Sedgipour, M. & Sadeghi-Bazargani, H. 2009. Contralateral eye comparison on changes in visual field following laser in situ keratomileusis vs photorefractive keratectomy for myopia: a randomized clinical trial. *Pakistan Journal of Biological Sciences,* 12(23)**,** 1521-1525.

Mrochen, M., Kaemmerer, M., Mierdel, P. & Seiler, T. 2001. Increased higher-order optical aberrations after laser refractive surgery: a problem of subclinical decentration. *Journal of Cataract & Refractive Surgery,* 27(3)**,** 362-369.

Müller, L., Pels, L. & Vrensen, G. 1996. Ultrastructural organization of human corneal nerves. *Investigative Ophthalmology & Visual Science,* 37(4)**,** 476-488.

Müller, L. J., Pels, E. & Vrensen, G. F. 2001. The specific architecture of the anterior stroma accounts for maintenance of corneal curvature. *British Journal of Ophthalmology,* 85(4)**,** 437-443.

Munnerlyn, C. R., Koons, S. J. & Marshall, J. 1988. Photorefractive keratectomy: a technique for laser refractive surgery. *Journal of Cataract and Refractive Surgery,* 14(1)**,** 46-52.

Muñoz, G., Albarrán-Diego, C. & Sakla, H. F. 2007. Validity of autorefraction after cataract surgery with multifocal ReZoom intraocular lens implantation. *Journal of Cataract & Refractive Surgery,* 33(9)**,** 1573-1578.

Munson, K., Hong, X. & Thibos, L. N. 2001. Use of a Shack-Hartmann aberrometer to assess the optical outcome of corneal transplantation in a keratoconic eye. *Optometry & Vision Science,* 78(12)**,** 866-871.

Musa, F., Tailor, R., Gao, A., Hutley, E., Rauz, S. & Scott, R. 2010. Contact lens-related microbial keratitis in deployed British military personnel. *British Journal of Ophthalmology,* 94(8), 988-993.

Nakaishi, H. & Yamada, Y. 1999. Abnormal tear dynamics and symptoms of eyestrain in operators of visual display terminals. *Occupational and Environmental Medicine,* 56(1)**,** 6-9.

Nakamura, K., Kurosaka, D., Bissen-Miyajima, H. & Tsubota, K. 2001. Intact corneal epithelium is essential for the prevention of stromal haze after laser assisted in situ keratomileusis. *British Journal of Ophthalmology,* 85(2)**,** 209-213.

Nam, J., Thibos, L. N., Bradley, A., Himebaugh, N. & Liu, H. 2011. Forward light scatter analysis of the eye in a spatially-resolved double-pass optical system. *Optics Express,* 19(8)**,** 7417-7438.

Navarro, R., Moreno-Barriuso, E. 1999. Laser ray-tracing method for optical testing. *Optics Letters,* 24(14)**,** 951-953.

Nemeth, J., Erdelyi, B., Csakany, B., Gaspar, P., Soumelidis, A., Kahlesh, F. & Lang, Z. 2002. High-speed videokeratoscopy measurement of tear film build-up time. *Investigative Ophthalmology and Visual Science,* 43(6)**,** 1783–1790.

Netto, M. V., Mohan, R. R., Ambrósio Jr, R., Hutcheon, A. E., Zieske, J. D. & Wilson, S. E. 2005. Wound healing in the cornea: a review of refractive surgery complications and new prospects for therapy. *Cornea,* 24(5)**,** 509-522.

Nichols, B., Dawson, C. & Togni, B. 1983. Surface features of the conjunctiva and cornea. *Investigative Ophthalmology & Visual Science,* 24(5)**,** 570-576.

Nichols, J. J., Ziegler, C., Mitchell, G. L. & Nichols, K. K. 2005. Self-reported dry eye disease across refractive modalities. *Investigative Ophthalmology & Visual Science,* 46(6)**,** 1911-1914.

Nichols, K. K., Nichols, J. J. & Mitchell, G. L. 2004a. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea,* 23(8)**,** 762-770.

Nichols, K. K., Nichols, J. J. & Mitchell, G. L. 2004b. The reliability and validity of McMonnies dry eye index. *Cornea,* 23(4)**,** 365-371.

Nichols, K. K., Nichols, J. J. & Zadnik, K. 2000. Frequency of dry eye diagnostic test procedures used in various modes of ophthalmic practice. *Cornea,* 19(4)**,** 477-482.

O'Brart, D., Lohmann, C., Fitzke, F., Smith, S., Kerr-Muir, M. & Marshall, J. 1994. Night vision after excimer laser photorefractive keratectomy: haze and halos. *European Journal of Ophthalmology,* 4(1)**,** 43-51.

O'Brien, T. P., Li, Q., Ashraf, M. F., Matteson, D. M., Stark, W. J. & Chan, C.-C. 1998. Inflammatory response in the early stages of wound healing after excimer laser keratectomy. *Archives of Ophthalmology,* 116(11)**,** 1470-1474.

O'Doherty, M., Kirwan, C., O'Keeffe, M. & O'Doherty, J. 2007. Postoperative pain following epi-LASIK, LASEK, and PRK for myopia. *Journal of Refractive Surgery,* 23(2)**,** 133-138.

O'Connor, A., Stephenson, T., Johnson, A., Tobin, M., Ratib, S. & Fielder, A. 2006. Change of refractive state and eye size in children of birth weight less than 1701 g. *British Journal of Ophthalmology,* 90(4)**,** 456-460.

Ockrim, Z., Yorston D., 2010. *British Medical Journal*, 341:c5400.

Ooi, T. L. & He, Z. J. 1999. Binocular rivalry and visual awareness: The role of attention. *Perception-London,* 28(5)**,** 551-574.

Oshika, T., Klyce, S. D., Applegate, R. A., Howland, H. C. & El Danasoury, M. A. 1999. Comparison of corneal wavefront aberrations after photorefractive keratectomy and laser in situ keratomileusis. *American Journal of Ophthalmology,* 127(1)**,** 1-7.

Owsley, C., Sekuler, R. & Boldt, C. 1981. Aging and low-contrast vision: face perception. *Investigative Ophthalmology & Visual Science,* 21(2)**,** 362-365.

Ozdamar, A., Küçüksümer, Y., Aras, C., Akova, N. & Ustundag, C. 2004. Visual field changes after laser in situ keratomileusis in myopic eyes. *Journal of Cataract & Refractive Surgery,* 30(5)**,** 1020-1023.

Pallikaris, I. G., Kymionis, G. D., Panagopoulou, S. I., Siganos, C. S., Theodorakis, M. A. & Pallikaris, A. I. 2002. Induced optical aberrations following formation of a laser in situ keratomileusis flap. *Journal of Cataract & Refractive Surgery,* 28(10)**,** 1737-1741.

Pallikaris, L. G., Papatzanaki, M. E., Stathi, E. Z., Frenschock, O. & Georgiadis, A. 1990. Laser in situ keratomileusis. *Lasers in Surgery and Medicine,* 10(5)**,** 463-468.

Papas, E. B., Decenzo-Verbeten, T., Fonn, D., Holden, B. A., Kollbaum, P. S., Situ, P., Tan, J. & Woods, C. 2009. Utility of short-term evaluation of presbyopic contact lens performance. *Eye & Contact Lens,* 35(3)**,** 144-148.

Patel, I. 2007. Presbyopia: prevalence, impact, and interventions. *Community Eye Health,* 20(63)**,** 40-41.

Pauly, A., Brignole-Baudouin, F., Guenoun, J. M., Riancho, L., Rat, P., Warnet, J. M. & Baudouin, C. 2007. Comparative study of topical anti-allergic eye drops on human conjunctiva-derived cells: responses to histamine and IFNγ and toxicological profiles. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 245(4)**,** 534-546.

Peckar, C. 1991. Extracapsular Techniques. *In:* Percival, S. P. (ed.) *A Colour Atlas of Lens Implantation.* Ayelsbury, UK: Wolfe Publishing Ltd.

Pelli, D., Robson, J. & Wilkins, A. 1988. The design of a new letter chart for measuring contrast sensitivity. *Clinical Vision Science,* 2(1)**,** 187-199.

Perez-Santonja, J. J., Bellot, J., Claramonte, P., Ismail, M. M. & Alio, J. L. 1997. Laser in situ keratomileusis to correct high myopia. *Journal of Cataract and Refractive surgery,* 23(3)**,** 372-385.

Pesudovs, K. & Weisinger, H. S. 2004. A comparison of autorefractor performance. *Optometry & Vision Science,* 81(7)**,** 554.

Pflugfelder, S. C. 2007. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *The Ocular Surface,* 5(2)**,** 163-178.

Pflugfelder, S. C. 2011. Tear dysfunction and the cornea: LXVIII Edward Jackson Memorial Lecture. *American Journal of Ophthalmology,* 152(6)**,** 900-909.

Pierscionek, B. & Weale, R. 1995. The optics of the eye-lens and lenticular senescence. *Documenta Ophthalmologica,* 89(4)**,** 321-335.

Piñero, D. P., Pérez-Cambrodí, R. J., Gómez-Hurtado, A., Blanes-Mompó, F. J. & Alzamora-Rodríguez, A. 2012. Results of laser in situ keratomileusis performed using solid-state laser technology. *Journal of Cataract and Refractive Surgery,* 38 (3)**,** 437-444.

Pisella, P. J., Debbasch, C., Hamard, P., Creuzot-Garcher, C., Rat, P., Brignole, F. & Baudouin, C. 2004. Conjunctival proinflammatory and proapoptotic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study. *Investigative Ophthalmology & Visual Science,* 45(5)**,** 1360-1368.

Plainis, S., Ntzilepis, G., Atchison, D. A. & Charman, W. N. 2013. Through-focus performance with multifocal contact lenses: effect of binocularity, pupil diameter and inherent ocular aberrations. *Ophthalmic and Physiological Optics,* 33(1)**,** 42-50.

Plainis, S., Petratou, D., Giannakopoulou, T., Atchison, D. A. & Tsilimbaris, M. K. 2011. Binocular summation improves performance to defocus-induced blur. *Investigative Ophthalmology & Visual Science,* 52(5)**,** 2784-2789.

Plakitsi, A. & Charman, W. N. 1995. Comparison of the depths of focus with the naked eye and with three types of presbyopic contact lens correction. *Journal of the British Contact Lens Association,* 18(4)**,** 119-125.

Pogorelov, P., Langenbucher, A., Kruse, F. & Seitz, B. 2006. Long-term results of phototherapeutic keratectomy for corneal map-dot-fingerprint dystrophy (Cogan-Guerry). *Cornea,* 25(7)**,** 774-777.

Polack, F. M. & Sugar, A. 1977. The phacoemulsification procedure. III. Corneal complications. *Investigative Ophthalmology & Visual Science,* 16(1)**,** 39-46.

Porter, J., Guirao, A., Cox, I. G. & Williams, D. R. 2001. Monochromatic aberrations of the human eye in a large population. *Journal of the Optical Society of America. A, Optics and Image Science,* 18(8)**,** 1793-1803.

Porter, J., MacRae, S., Yoon, G., Roberts, C., Cox, I. G. & Williams, D. R. 2003. Separate effects of the microkeratome incision and laser ablation on the eye's wave aberration. *American Journal of Ophthalmology,* 136(2)**,** 327-337.

Potgieter, F. J., Roberts, C., Cox, I. G., Mahmoud, A. M., Herderick, E. E., Roetz, M. & Steenkamp, W. 2005. Prediction of flap response. *Journal of Cataract & Refractive Surgery,* 31(1)**,** 106-114.

Pujol, J., Gispets, J. & Arjona, M. 2003. Optical performance in eyes wearing two multifocal contact lens designs. *Ophthalmic and Physiological Optics,* 23(4)**,** 347-360.

Pult, H., Gill, F. & Riede-Pult, B. H. 2012. Effect of three different liposomal eye sprays on ocular comfort and tear film. *Contact Lens and Anterior Eye,* 35(5), 203-207.

Qazi, M. A., Pepose, J. S., & Shuster, J. J. (2002). Implantation of scleral expansion band segments for the treatment of presbyopia. *American journal of ophthalmology*, *134*(6), 808-815.

Rainer, G., Findl, O., Petternel, V., Kiss, B., Drexler, W., Skorpik, C., Georgopoulos, M. & Schmetterer, L. 2004. Central corneal thickness measurements with partial coherence interferometry, ultrasound, and the Orbscan system. *Ophthalmology,* 111(5)**,** 875-879.

Raj, P. S., Villada, J. R., Myint, K., Lewis, A. & Akingbehin, T. 1991. Clinical evaluation of automated refraction in anterior chamber pseudophakia. *British Journal of Ophthalmology,* 75(1)**,** 42-44.

Ramón, M. L., Piñero, D. P. & Pérez-Cambrodí, R. J. 2012. Correlation of Visual Performance With Quality of Life and Intraocular Aberrometric Profile in Patients Implanted With Rotationally Asymmetric Multifocal IOLs. *Journal of Refractive Surgery,* 28(2)**,** 93-99.

Rasp, M., Bachernegg, A., Seyeddain, O., Ruckhofer, J., Emesz, M., Stoiber, J., Grabner, G. & Dexl, A. K. 2012. Bilateral reading performance of 4 multifocal intraocular lens models and a monofocal intraocular lens under bright lighting conditions. *Journal of Cataract and Refractive Surgery,* 38(11)**,** 1950-1961.

Rauscher, F. M., Sekhon, N., Feuer, W. J. & Budenz, D. L. 2009. Myopia affects retinal nerve fiber layer measurements as determined by optical coherence tomography. *Journal of Glaucoma,* 18(7)**,** 501-505.

Reinstein, D. Z., Silverman, R. H., Sutton, H. F. & Coleman, D. J. 1999. Very high-frequency ultrasound corneal analysis identifies anatomic correlates of optical complications of lamellar refractive surgery: Anatomic diagnosis in lamellar surgery. *Ophthalmology,* 106(3)**,** 474-482.

Ren, Q., Simon, G., Legeais, J.M., Parel, J.M., Culbertson, W., Shen, J., Takesue, Y. & Savoldelli, M. 1994. Ultraviolet solid-state laser (213-nm) photorefractive keratectomy. In vivo study. *Ophthalmology,* 101(5)**,** 883-889.

Richdale, K., Mitchell, G. & Zadnik, K. 2006. Comparison of multifocal and monovision soft contact lens corrections in patients with low-astigmatic presbyopia. *Optometry and Vision Science: official publication of the American Academy of Optometry,* 83(5)**,** 266-273.

Richdale, K., Sinnott, L. T., Skadahl, E. & Nichols, J. J. 2007. Frequency of and factors associated with contact lens dissatisfaction and discontinuation. *Cornea,* 26(2)**,** 168-174.

Ridder III, W. H., LaMotte, J., Hall Jr, J. Q., Sinn, R., Nguyen, A. L. & Abufarie, L. 2009. Contrast sensitivity and tear layer aberrometry in dry eye patients. *Optometry & Vision Science,* 86(9)**,** 1059-1068.

Robman, L. & Taylor, H. 2005. External factors in the development of cataract. *Eye,* 19(10)**,** 1074-1082.

Rocha, K. M., Vabre, L., Chateau, N. & Krueger, R. R. 2009. Expanding depth of focus by modifying higher-order aberrations induced by an adaptive optics visual simulator. *Journal of Cataract and Refractive Surgery*, 35(11)**,** 1885-1892.

Rodríguez Pérez, P., Navarro, R., Arines, J. & Bará, S. 2006. A calibration set for ocular aberrometers: Manufacture, testing and application. *Journal of Refractive Surgery*, 22(3), 275-284.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Adams, R. J., Berry, J. D., Brown, T. M., Carnethon, M. R., Dai, S., de Simone, G. & Ford, E. S. 2011. Executive Summary: Heart Disease and Stroke Statistics—2011 Update A Report From the American Heart Association. *Circulation,* 123(4)**,** 459-463.

Rolando, M., Geerling, G., Dua, H., Benítez-del-Castillo, J. & Creuzot-Garcher, C. 2010. Emerging treatment paradigms of ocular surface disease: proceedings of the Ocular Surface Workshop. *British Medical Journal,* 94**,** Suppl 1: 1-9

Rosén, R., Jaeken, B., Lindskoog Petterson, A., Artal, P., Unsbo, P. & Lundström, L. 2012. Evaluating the peripheral optical effect of multifocal contact lenses. *Ophthalmic and Physiological Optics,* 32(6)**,** 527-534.

Roszkowska, A. M., De Grazia, L., Ferreri, P. & Ferreri, G. 2006. One-year clinical results of photorefractive keratectomy with a solid-state laser for refractive surgery. *Journal of Refractive Surgery,* 22(6)**,** 611-613.

Rozema, J. J., Coeckelbergh, T., Van den Berg, T. J., Trau, R., Duchateau, N. C., Lemmens, S. & Tassignon, M.-J. 2010. Straylight before and after LASEK in myopia: changes in retinal straylight. *Investigative Ophthalmology & Visual Science,* 51(5)**,** 2800-2804.

Rozema, J. J., Van Dyck, D. E. & Tassignon, M.-J. 2006. Clinical comparison of 6 aberrometers Part 2: Statistical comparison in a test group. *Journal of Cataract & Refractive Surgery,* 32(1)**,** 33-44.

Rsdeep, D. E. & De Catarata, P. 2006. Systematic review of population-based studies of the prevalence of cataracts. *Archivos de la Sociedad Espanola de Oftalmologica,* 81(9)**,** 509-516.

Rüfer, F., Schröder, A. & Erb, C. 2005. White-to-white corneal diameter: normal values in healthy humans obtained with the Orbscan II topography system. *Cornea,* 24(3)**,** 259-261.

Ruskell, G. 1974. Ocular fibres of the maxillary nerve in monkeys. *Journal of Anatomy,* 118 (Pt 2)**,** 195-203.

Sakimoto, T., Rosenblatt, M. I. & Azar, D. T. 2006. Laser eye surgery for refractive errors. *Lancet,* 367(9520)**,** 1432-1447.

Salmon, T. O. & van de Pol, C. 2006. Normal-eye Zernike coefficients and root-mean-square wavefront errors. *Journal of Cataract & Refractive Surgery,* 32(12)**,** 2064-2074.

Salmon, T. O., West, R. W., Gasser, W. & Kenmore, T. 2003. Measurement of refractive errors in young myopes using the COAS Shack-Hartmann aberrometer. *Optometry & Vision Science,* 80(1)**,** 6-14.

Savini, G., Barboni, P., Parisi, V. & Carbonelli, M. 2012. The influence of axial length on retinal nerve fibre layer thickness and optic-disc size measurements by spectral-domain OCT. *British Journal of Ophthalmology,* 96(1)**,** 57-61.

Schallhorn, S. C., Kaupp, S. E., Tanzer, D. J., Tidwell, J., Laurent, J. & Bourque, L. B. 2003. Pupil size and quality of vision after LASIK. *Ophthalmology,* 110(8)**,** 1606-1614.

Schiffman, R. M., Christianson, M. D., Jacobsen, G., Hirsch, J. D. & Reis, B. L. 2000. Reliability and validity of the ocular surface disease index. *Archives of Ophthalmology,* 118(5)**,** 615-621.

Schor, C., Landsman, L. & Erickson, P. 1987. Ocular dominance and the interocular suppression of blur in monovision. *American Journal of Optometry and Physiological Optics,* 64(10)**,** 723-730.

Seider, M. I., McLeod, S. D., Porco, T. C. & Schallhorn, S. C. 2013. The Effect of Procedure Room Temperature and Humidity on LASIK Outcomes. *Ophthalmology*, S0161-6420.

Sekhar, G. C., Naduvilath, T. J., Lakkai, M., Jayakumar, A. J., Pandi, G. T., Mandal, A. K. & Honavar, S. G. 2000. Sensitivity of Swedish interactive threshold algorithm compared with standard full threshold algorithm in Humphrey visual field testing. *Ophthalmology,* 107(7)**,** 1303-1308.

Shah, S., Sarhan, A. S., Doyle, S., Pillai, C. & Dua, H. 2001. The epithelial flap for photorefractive keratectomy. *British Journal of Ophthalmology,* 85(4)**,** 393-396.

Shah, S., Sheppard, A. L., Castle, J., Baker, D., Buckhurst, P. J., Naroo, S. A., Davies, L. N. & Wolffsohn, J. S. 2012. Refractive outcomes of laser-assisted subepithelial keratectomy for myopia, hyperopia, and astigmatism using a 213 nm wavelength solid-state laser. *Journal of Cataract & Refractive Surgery,* 38(5)**,** 746-751.

Sharma, M., Wachler, B. & Chan, C. 2007. Higher order aberrations and relative risk of symptoms after LASIK. *Journal of refractive surgery*, 23(3)**,** 252-256.

Sheppard, A. L. & Davies, L. N. 2010. Clinical evaluation of the Grand Seiko Auto Ref/Keratometer WAM-5500. *Ophthalmic and Physiological Optics,* 30(2)**,** 143-151.

Sheppard, A. L. & Davies, L. N. 2011. The effect of ageing on in vivo human ciliary muscle morphology and contractility. *Investigative Ophthalmology & Visual Science,* 52(3)**,** 1809-1816.

Shneor, E., Millodot, M., Avraham, O., Amar, S. & Gordon-Shaag, A. 2011. Clinical evaluation of the L80 autorefractometer. *Clinical and Experimental Optometry*, 95(1), 66-71.

Shoja, M. & Besharati, M. 2007. Dry eye after LASIK for myopia: Incidence and risk factors. *European Journal of Ophthalmology,* 17(1)**,** 1-6.

Shortt, A. J., Bunce, C. & Allan, B. 2006. Evidence for superior efficacy and safety of LASIK over photorefractive keratectomy for correction of myopia. *Ophthalmology,* 113(11)**,** 1897-1908.

Smith, J., Nichols, K. K. & Baldwin, E. K. 2008. Current patterns in the use of diagnostic tests in dry eye evaluation. *Cornea,* 27(6)**,** 656-662.

Smith, J. A. 2007. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *The Ocular Surface,* 5(2)**,** 93-107.

Smith, R. J. & Maloney, R. K. 1998. Diffuse lamellar keratitis: A new syndrome in lamellar refractive surgery. *Ophthalmology,* 105(9)**,** 1721-1726.

Solomon, K. D., Fernández de Castro, L. E., Sandoval, H. P., Biber, J. M., Groat, B., Neff, K. D., Ying, M. S., French, J. W., Donnenfeld, E. D. & Lindstrom, R. L. 2009.

LASIK world literature review: quality of life and patient satisfaction. *Ophthalmology,* 116(4)**,** 691-701.

Sparrow, J., Bron, A., Brown, N., Ayliffe, W. & Hill, A. 1986. The Oxford clinical cataract classification and grading system. *International Ophthalmology,* 9(4)**,** 207-225.

Stafford, M. J. (2001). The histology and biology of the lens. Optometry Today. 41(1), 23-30.

Stanley, P. F., Tanzer, D. J. & Schallhorn, S. C. 2008. Laser refractive surgery in the United States Navy. *Current Opinion in Ophthalmology,* 19(4)**,** 321-324.

Steinert, R. F., Aker, B. L., Trentacost, D. J., Smith, P. J. & Tarantino, N. 1999. A prospective comparative study of the AMO ARRAY zonal-progressive multifocal silicone intraocular lens and a monofocal intraocular lens. *Ophthalmology,* 106(7)**,** 1243-1255.

Stramer, B. M., Zieske, J. D., Jung, J.-C., Austin, J. S. & Fini, M. E. 2003. Molecular mechanisms controlling the fibrotic repair phenotype in cornea: implications for surgical outcomes. *Investigative Ophthalmology & Visual Science,* 44(10)**,** 4237-4246.

Strang, N. C., Gray, L. S., Winn, B., & Pugh, J. R. (1998). Clinical evaluation of patient tolerance to autorefractor prescriptions. *Clinical and experimental optometry*, *81*(3), 112-118.

Suryakumar, R. & Bobier, W. 2003. The manifestation of noncycloplegic refractive state in pre-school children is dependent on autorefractor design. *Optometry & Vision Science,* 80(8)**,** 578-586.

Tafreshi, A., Racette, L., Weinreb, R. N., Sample, P. A., Zangwill, L. M., Medeiros, F. A., & Bowd, C. (2010). Pattern electroretinogram and psychophysical tests of visual function for discriminating between healthy and glaucoma eyes. *American journal of ophthalmology*, *149*(3), 488-495.

Teichman, J. C., Vold, S. D. & Ahmed, I. I. K. 2012. Top 5 Pearls for Implanting Premium IOLs in Patients With Glaucoma. *International Ophthalmology Clinics,* 52(2)**,** 65-71.

Thai, L. C., Tomlinson, A. & Ridder III, W. H. 2002. Contact lens drying and visual performance: the vision cycle with contact lenses. *Optometry & Vision Science,* 79(6)**,** 381-388.

Thibos, L. & Hong, X. 1999. Clinical applications of the Shack-Hartmann aberrometer. *Optometry and Vision Science,* 76(12)**,** 817-825.

Thibos, L. N. 2001. Wavefront data reporting and terminology. *Journal of Refractive Surgery,* 17(5)**,** 578-583.

Thibos, L. N., Applegate, R. A., Schwiegerling, J. T. & Webb, R. 2002a. Standards for reporting the optical aberrations of eyes. *Journal of Refractive Surgery,* 18(5)**,** S652-S660.

Thibos, L. N., Bradley, A. & Hong, X. 2002b. A statistical model of the aberration structure of normal, well-corrected eyes. *Ophthalmic and Physiological Optics,* 22(5)**,** 427-433.

Thibos, L. N., Wheeler, W. & Horner, D. 1997. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optometry and*

vision science: official publication of the American Academy of Optometry, 74(6)**,** 367-375.

Thylefors, B., Chylack Jr, L., Konyama, K., Sasaki, K., Sperduto, R., Taylor, H. & West, S. 2002. A simplified cataract grading system The WHO Cataract Grading Group. *Neuro-Ophthalmology,* 9(2)**,** 83-95.

Ti, S.E., Chee, S.P., Tan, D. T., Yang, Y.N. & Shuang, S. L. 2013. Descemet Membrane Detachment After Phacoemulsification Surgery: Risk Factors and Success of Air Bubble Tamponade. *Cornea,* 32(4)**,** 454-459.

Toivanen, M., Tervo, T., Partanen, M., Vannas, A. & Hervonen, A. 1987. Histochemical demonstration of adrenergic nerves in the stroma of human cornea. *Investigative Ophthalmology & Visual Science,* 28(2)**,** 398-400.

Topouzis, F., Wilson, M. R., Harris, A., Founti, P., Yu, F., Anastasopoulos, E., Pappas, T., Koskosas, A., Salonikiou, A. & Coleman, A. L. 2011. Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki eye study. *American Journal of Ophthalmology,* 152(2)**,** 219-228.

Townley, D., Kirwan, C. & O'Keefe, M. 2012. One year follow-up of contrast sensitivity following conventional laser in situ keratomileusis and laser epithelial keratomileusis. *Acta Ophthalmologica,* 90(1)**,** 81-85.

Tran, D. B., Sarayba, M. A., Bor, Z., Garufis, C., Duh, Y. J., Soltes, C. R., Juhasz, T. & Kurtz, R. M. 2005. Randomized prospective clinical study comparing induced aberrations with IntraLase and Hansatome flap creation in fellow eyes: potential impact on wavefront-guided laser in situ keratomileusis. *Journal of Cataract and Refractive Surgery,* 31(1)**,** 97-105.

Tripathi, B. & Tripathi, R. 1989. Cytotoxic effects of benzalkonium chloride and chlorobutanol on human corneal epithelial cells in vitro. *Lens and Eye Toxicity Research,* 6(3)**,** 395-403.

Trokel, S. L., Srinivasan, R. & Braren, B. 1983. Excimer laser surgery of the cornea. *American Journal of Ophthalmology,* 96(6)**,** 710-715.

Trueb, P. R., Albach, C., Montés-Micó, R. & Ferrer-Blasco, T. 2009. Visual acuity and contrast sensitivity in eyes implanted with aspheric and spherical intraocular lenses. *Ophthalmology,* 116(5)**,** 890-895.

Tsiklis, N. S., Kymionis, G. D., Kounis, G. A., Pallikaris, A. I., Diakonis, V. F., Charisis, S., Markomanolakis, M. M. & Pallikaris, I. G. 2007a. One-year results of photorefractive keratectomy and laser in situ keratomileusis for myopia using a 213 nm wavelength solid-state laser. *Journal of Cataract & Refractive Surgery,* 33(6)**,** 971-977.

Tsiklis, N. S., Kymionis, G. D., Pallikaris, A. I., Diakonis, V. F., Ginis, H. S., Kounis, G. A., Panagopoulou, S. I. & Pallikaris, I. G. 2007b. Endothelial cell density after photorefractive keratectomy for moderate myopia using a 213 nm solid-state laser system. *Journal of Cataract & Refractive Surgery,* 33(11)**,** 1866-1870.

Tsubota, K., Kawashima, M., Inaba, T., Dogru, M., Matsumoto, Y., Ishida, R., Kaido, M., Kojima, T., Uchino, M. & Uchino, Y. 2012. The Antiaging Approach for the Treatment of Dry Eye. *Cornea,* 31(11)**,** S3-S8.

Tung, C. I., Kottaiyan, R., Koh, S., Wang, Q., Yoon, G., Zavislan, J. M., Davio, S. R. & Aquavella, J. V. 2012. Noninvasive, Objective, Multimodal Tear Dynamics Evaluation of

5 Over-the-Counter Tear Drops in a Randomized Controlled Trial. *Cornea,* 31(2)**,** 108-114.

Tutt, R., Bradley, A., Begley, C. & Thibos, L. N. 2000. Optical and visual impact of tear break-up in human eyes. *Investigative Ophthalmology & Visual Science,* 41(13)**,** 4117-4123.

United Kingdom National Statistics. Population Ageing in the United Kingdom, its Constituent Countries and the European Union. Accessed at: http://www.ons.gov.uk/ons/dcp171776_258607.pdf, accessed on June 24th 2013.

United Kingdom Natonal Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2011 and Mid-2012. Accessed at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-319259, accessed on September 24th

van de Pol, C., Soya, K. & Hwang, D. G. 2001. Objective assessment of transient corneal haze and its relation to visual performance after photorefractive keratectomy. *American Journal of Ophthalmology,* 132(2)**,** 204-210.

Vesaluoma, M. H., Petroll, W. M., Pérez-Santonja, J. J., Valle, T. U., Alió, J. L. & Tervo, T. M. 2000. Laser in situ keratomileusis flap margin: wound healing and complications imaged by in vivo confocal microscopy. *American Journal of Ophthalmology,* 130(5)**,** 564-573.

Villada, J. R., Raj, P. S., Lewis, A. E., Joyce, P. W. & Watson, A. 1992. Comparative evaluation of the Allergan Humphrey 570 and Canon RK-1 autorefractors: II objective autorefraction in pseudophakes. *Eye*, 6(Pt 3)**,** 287-289.

Vinciguerra, P., Camesasca, F. I. & Randazzo, A. 2003. One-year results of butterfly laser epithelial keratomileusis. *Journal of Refractive Surgery,* 19 (2 Suppl)**,** S223-S226.

Vingolo, E. M., Grenga, P. L., Iacobelli, L. & Grenga, R. 2007. Visual acuity and contrast sensitivity: AcrySof ReSTOR apodized diffractive versus AcrySof SA60AT monofocal intraocular lenses. *Journal of Cataract and Refractive Surgery,* 33(7)**,** 1244-1247.

Vitale, S., Goodman, L. A., Reed, G. F. & Smith, J. A. 2004. Comparison of the NEI-VFQ and OSDI questionnaires in patients with Sjögren's syndrome-related dry eye. *Health and Quality of Life Outcomes,* 2**,** 44.

Walsh, G., Charman, WN, Howland, HC 1984. Objective technique for the determination of monochromatic aberrations of the eye. *Journal of the Optical Society of America. A, Optics and Image Science,* 1(9)**,** 987-982.

Walter, K. A. & Stevenson, A. W. 2004. Effect of environmental factors on myopic LASIK enhancement rates. *Journal of Cataract & Refractive Surgery,* 30(4)**,** 798-803.

Wang, B. & Ciuffreda, K. J. 2006. Depth-of-focus of the human eye: theory and clinical implications. *Survey of Ophthalmology,* 51(1)**,** 75-85

Wang, L. & Koch, D. D. 2003. Ocular higher-order aberrations in individuals screened for refractive surgery. *Journal of Cataract & Refractive Surgery,* 29(10)**,** 1896-1903.

Watanabe, H., Fabricant, M., Tisdale, A. S., Spurr-Michaud, S. J., Lindberg, K. & Gipson, I. 1995. Human corneal and conjunctival epithelia produce a mucin-like glycoprotein for the apical surface. *Investigative Ophthalmology & Visual Science,* 36(2)**,** 337-344.

Weinreb, R. & Perlman, J. 1986. The effect of refractive correction on automated perimetric thresholds. *American Journal of Ophthalmology,* 101(6)**,** 706-709.

Weiss, J. S. 2007. Visual morbidity in thirty-four families with Schnyder crystalline corneal dystrophy (an American Ophthalmological Society thesis). *Transactions of the American Ophthalmological Society,* 105**,** 616-648.

Wild, J. M., Pacey, I. E., Hancock, S. A. & Cunliffe, I. A. 1999. Between-algorithm, between-individual differences in normal perimetric sensitivity: full threshold, FASTPAC, and SITA. Swedish Interactive Threshold algorithm. *Investigative Ophthalmology and Visual Science,* 40**,** 1152-1161.

Williams, C., Miller, L., Northstone, K. & Sparrow, J. 2008. The use of non-cycloplegic autorefraction data in general studies of children's development. *British journal of Ophthalmology,* 92(5)**,** 723-724.

Wilson, S. E. 1998. LASIK: management of common complications. *Cornea,* 17(5)**,** 459-467.

Wilson, S. E. & Hong, J.-W. 2000. Bowman's layer structure and function: critical or dispensable to corneal function? A hypothesis. *Cornea,* 19(4)**,** 417-420.

Win-Hall, D. M., Houser, J. & Glasser, A. 2010. Static and Dynamic Measurement of Accommodation Using the Grand Seiko WAM-5500 Autorefractor. *Optometry and vision science: official publication of the American Academy of Optometry,* 87(11)**,** 873-882.

Wolffsohn, J., Gilmartin, B., Mallen, E. A. & Tsujimura, S. 2001. Continuous recording of accommodation and pupil size using the Shin-Nippon SRW-5000 autorefractor. *Ophthalmic and Physiological Optics,* 21(2)**,** 108-113.

Wood, I. 1987. A review of autorefractors. *Eye,* 1(Pt 4)**,** 529-535.

Wood, J. M., Wild, J. M., Bullimore, M. A. & Gilmartin, B. 1988. Factors affecting the normal perimetric profile derived by automated static threshold LED perimetry. I. Pupil size. *Ophthalmic and Physiological Optics,* 8(1)**,** 26-31.

Wood, J. M., Wild, J. M., Hussey, M. K. & Crews, S. J. 1987. Serial examination of the normal visual field using Octopus automated projection perimetry evidence for a learning effect. *Acta Ophthalmologica,* 65(3)**,** 326-333.

Woods, R. L., Colvin, C. R., Vera-Diaz, F. A. & Peli, E. 2010. A relationship between tolerance of blur and personality. *Investigative Ophthalmology & Visual Science,* 51(11)**,** 6077-6082.

Woodward, M. A. & Edelhauser, H. F. 2011. Corneal endothelium after refractive surgery. *Journal of Cataract & Refractive Surgery,* 37(4)**,** 767-777.

World Health Organization. 2010. Available at http://www.who.int/blindness/causes/priority/en/index1.html accessed September 24th 2013

Xu, J., Bao, J., Deng, J., Lu, F. & He, J. C. 2011. Dynamic changes in ocular Zernike aberrations and tear menisci measured with a wavefront sensor and an anterior segment OCT. *Investigative Ophthalmology & Visual Science,* 52(8)**,** 6050-6056.

Yamane, N., Miyata, K., Samejima, T., Hiraoka, T., Kiuchi, T., Okamoto, F., Hirohara, Y., Mihashi, T. & Oshika, T. 2004. Ocular higher-order aberrations and contrast

sensitivity after conventional laser in situ keratomileusis. *Investigative Ophthalmology & Visual Science,* 45(11)**,** 3986-3990.

Yang, X., Wang, Y., Zhao, K., & Fang, L. (2011). Comparison of higher-order aberration and optical quality after Epi-LASIK and LASIK for myopia. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *249*(2), 281-288.

Yau, J. W., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., Chen, S. J., Dekker, J. M., Fletcher, A. & Grauslund, J. 2012. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care,* 35(3)**,** 556-564.

Yee, R., Matsuda, M., Schultz, R. & Edelhauser, H. 1985. Changes in the normal corneal endothelial cellular pattern as a function of age. *Current eye research,* 4(6)**,** 671.

Yi, D. H. & Dana, M. R. Year. Corneal edema after cataract surgery: incidence and etiology. *In:* Seminars in Ophthalmology, 2002, 17(3-4), 110-114.

Yokoi, N., Yamada, H., Mizukusa, Y., Bron, A. J., Tiffany, J. M., Kato, T. & Kinoshita, S. 2008. Rheology of Tear Film Lipid Layer Spread in Normal and Aqueous Tear–Deficient Dry Eyes. *Investigative Ophthalmology & Visual Science,* 49(12)**,** 5319-5324.

Yoshino, M., Inoue, M., Kitamura, N. & Bissen-Miyajima, H. 2010. Diffractive multifocal intraocular lens interferes with intraoperative view. *Clinical Ophthalmology (Auckland, NZ),* 4**,** 467-469.

Zhang L, Pelli DG & JG., R. 1989. The effects of luminance, distance, and defocus on contrast sensitivity as measured by the Pelli-Robson chart. *Investigative Ophthalmology & Visual Science,* 30**,** 406.

Zhang, X., Ye, M., Bradley, A. & Thibos, L. 1999. Apodization by the Stiles-Crawford effect moderates the visual impact of retinal image defocus. *Journal of the Optical Society of America A, Optics and Image Science,* 16(9)**,** 812-820.

Zhao, J., Mao, J., Luo, R., Li, F., Pokharel, G. P. & Ellwein, L. B. 2004. Accuracy of noncycloplegic autorefraction in school-age children in China. *Optometry & Vision Science,* 81(1)**,** 49-55.

Zieske, J. D., Guimarães, S. R. & Hutcheon, A. E. 2001. Kinetics of keratocyte proliferation in response to epithelial debridement. *Experimental Eye Research,* 72(1)**,** 33-39.

APPENDIX 1

Dry eye questionnaire (Chapter 3)

DEQ 5

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, **how often** did your eyes feel discomfort?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   b. When your eyes felt discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

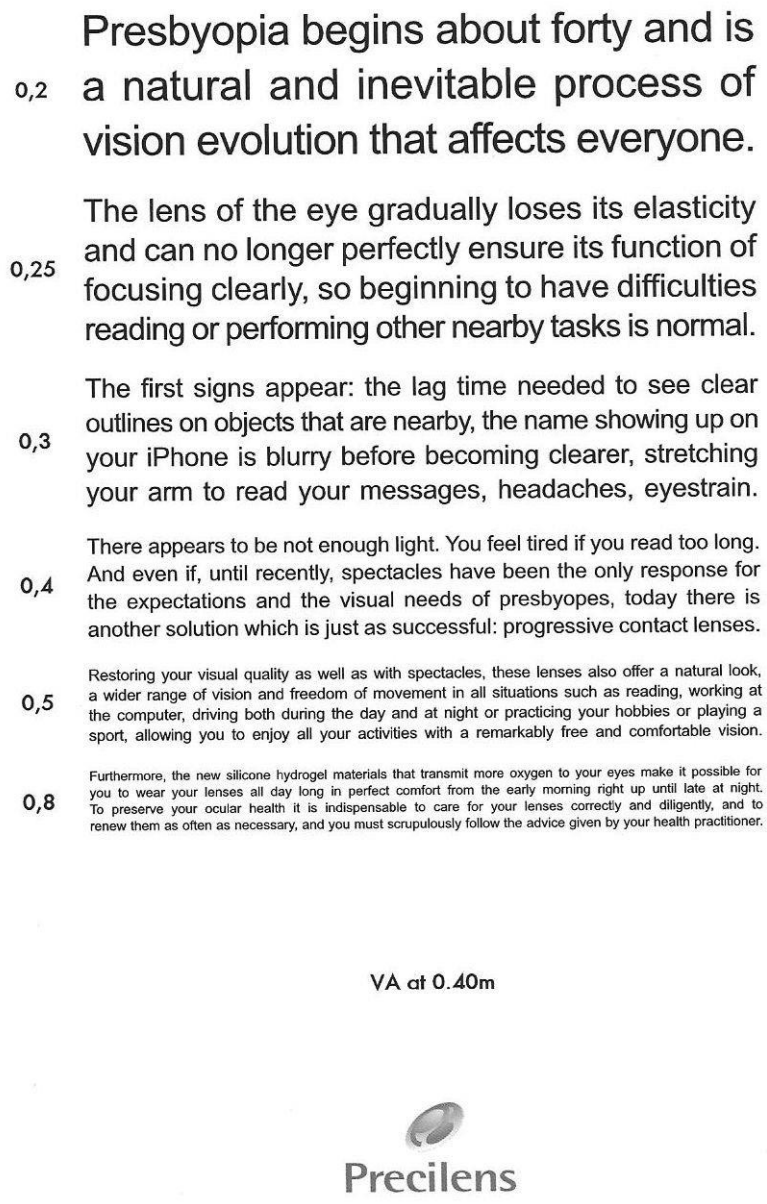
3. Question about **WATERY EYES:**
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?

      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total
___+___+___+___+___= ___

APPENDIX 2

Precilens reading chart (Chapters 5 and 6).



APPENDIX 3

Supporting publications:

- McGinnigle, S., Naroo, S. A. & Eperjesi, F. 2012. Evaluation of dry eye. *Survey of Ophthalmology,* 57(4)**,** 293-316 (copy attached).
- McGinnigle, S., Naroo, S. A. & Eperjesi, F. 2012. Optometric Management of Dry Eye available at http://www.optometry.co.uk/clinical/details?aid=876 (copy attached).
- McGinnigle, S., Naroo, S. A. & Eperjesi, F. 2013. Evaluations of the auto-refractor function of the Nidek OPD-Scan III. Clinical and Experimental Optometry: In press
- McGinnigle, S., Naroo, S. A. & Eperjesi, F. 2013. The Immediate effect of ocular lubricants on higher order aberrations and self-reported comfort in normal and dry eye. Contact Lens and Anterior Eye: In press.

Additional supporting material:

- Postgraduate Certificate with distinction in Optometry awarded in March 2013.
- Modules included were Research Methods (including statistical techniques), Ocular Therapeutics and Advanced Ophthalmic Examination.