2020

CLINICAL OUTCOMES POST-IMPLANTATION OF MULTIFOCAL AND TORIC INTRAOCULAR LENSES

Law, Elizabeth Martha

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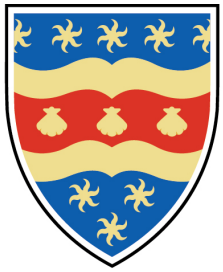

UNIVERSITY OF PLYMOUTH

CLINICAL OUTCOMES POST-IMPLANTATION OF MULTIFOCAL AND TORIC INTRAOCULAR LENSES

by

ELIZABETH MARTHA LAW

A thesis submitted to the University of Plymouth in partial fulfilment for the degree of

DOCTOR OF PHILOSOPHY

School of Health Professions

August 2020

Acknowledgements

First and foremost, I would like to thank all staff at the BMI Southend Hospital for their support throughout the studies. Particular thanks to Professor Rajesh Aggarwal and Mr Sam Kasaby, without whom none of this would be possible. I have been very privileged to work alongside such skilled ophthalmic surgeons and I hope I have absorbed at least a fraction of their clinical knowledge along the way. I would also like to thank Amanda Dunn, Angie Wilkinson and Lisa Wallis for their assistance in scheduling surgeries and patient appointments.

I must also thank my supervisors Professor Phillip Buckhurst, Dr Hetal Buckhurst, Professor Jonathan Marsden and Professor Gary Shum for their expertise, advice and guidance throughout. My gratitude also to Dr Catriona Hamer, my fellow Scot and ESCRS buddy, who I met when embarking on this journey, and who has offered great advice and support along the way. I will be forever thankful to her for stepping in when unforeseen circumstances required. My thanks also to the University of Plymouth for sponsoring my PhD and allowing me such an opportunity. Thanks also to Medicontur, Rayner and Carl Zeiss Meditec for the provision of intraocular lenses.

A special thank you to Kane Coeur-de-Lion Chung, for his help with the IOL illustrations throughout. He undoubtedly saved me weeks and weeks of wrangling with drawings.

To my family, I apologise for all the missed occasions and visits north of the border. I look forward to seeing you much more often now. To my work family, Alex Landells and Laura Roberts who supported me daily with endless cups of tea, chocolate bourbons and the occasional dose of tough love. Their unwavering dedication to their jobs, makes it so much easier to do mine.

Finally, and most importantly to Colin, who gave me the time and the space needed to get this done. For never complaining nor criticising, despite the endless lost evenings and weekends. He has kept me smiling throughout.

Author's Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee. Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment. This study was financed with the aid of a studentship from the University of Plymouth

The following external institution was visited for research and consultation purposes:

BMI Southend Hospital, 17 Fairfax Drive, Westcliff on Sea, Essex, SS0 9AG

Publications:

1. Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **Visual function and subjective perception of vision following bilateral implantation of monofocal and multifocal intraocular lenses: Randomised controlled trial.** *J Cataract Refract Surg*. 2020; 46:1020-1029.
2. Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **Optimising curve fitting techniques to enable standardised analysis of defocus curves derived from multifocal intraocular lenses**. *J Cataract Refract Surg*. Under Review
3. Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **Exploring clinical methods for predicting the post-operative addition power of a multifocal intraocular lens at the spectacle plane.** *J Refract Surg*. Under Review
4. Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **A randomised intra-patient comparison of closed loop and plate haptic toric intraocular lenses in patients with bilateral astigmatism.** *J Refract Surg.* Under Review
5. Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **One-year post-operative comparison of visual function and patient satisfaction with trifocal and extended depth of focus intraocular lenses** *J Refract Surg*. Under Review

Presentations and Posters:

6. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2015) **Assessment of dysphotopsia following implantation with trifocal intraocular lenses**. *Proceedings of the XXXIII congress of the European Society of Cataract and Refractive surgery.* Free Paper

7. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2016) **Initial outcomes following implantation of the Tecnis Symfony intraocular lens**. *Proceedings of the congress of the British Society for Refractive surgery.* Free Paper
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9. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2017) **Randomised Clinical Trial of BiFlex M Multifocal intraocular lens; preliminary results** *Proceedings of the XXXV congress of the European Society of Cataract and Refractive surgery.* Free Paper.
10. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2018) **Assessing and predicting the effective addition power of multifocal intraocular lenses**. *Proceedings of the Association for Research in vision and ophthalmology.* Poster
11. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2018) **Assessing and predicting the effective addition power of multifocal intraocular lenses**. *Proceedings of the British society for Refractive surgery.* Free Paper
12. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2019) **Visual function and spectacle independence following bilateral implantation of and multifocal intraocular lenses.** *Proceedings of the British society for Refractive surgery.* Free Paper.
13. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2019) **Assessing and predicting the effective addition power of multifocal intraocular lenses**. *Proceedings of the XXXVII congress of the European society for cataract and refractive surgery.* Free Paper
14. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2019) **Visual function and spectacle independence following bilateral implantation of monofocal and multifocal intraocular lenses: A randomised control trial.** *Proceedings of the XXXVII congress of the European society for cataract and refractive surgery.* E-Poster
15. Law, E.M., Aggarwal, R.K., Buckhurst, P.J., Kasaby, H.E., Buckhurst, H. (2020) **Randomised intra-patient comparison of closed loop and plate haptic toric intraocular lenses in patients with bilateral astigmatism.** *Proceedings of the XXIV Winter congress of the European society for cataract and refractive surgery.* E-Poster
16. Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **Optimising curve fitting techniques to enable standardised analysis of defocus curves derived from multifocal intraocular lenses**. Accepted for presentation at the *Proceedings of the XXXVIII congress of the European society for cataract and refractive surgery.* Free Paper

Word count of main body of thesis: 62,047

Signed:  Date: 31/08/2020

Abstract

Clinical outcomes post-implantation of multifocal and toric intraocular lenses

Elizabeth Martha Law
August 2020

In order to increase spectacle independence following cataract surgery and intraocular lens (IOL) implantation; correction of spherical refractive error, astigmatic error and presbyopia should all be given careful consideration. There are many premium IOLs, including multifocal intraocular lenses (MIOLs) and toric intraocular lenses (TIOLs), available to surgeons. In order to select the appropriate IOL to meet a patient's lifestyle and expectations, clinicians must fully understand the characteristics of MIOL and TIOL designs. To date, there remain unanswered questions pertaining to MIOLs and TIOLs and by rigorous comparison of such lenses, this thesis aims to address some of the gaps in the current literature.

This thesis aims to evaluate a robust protocol for investigating clinical outcomes in MIOLs that would allow for comparison between future studies. This methodology was used in a randomised control trial and a cohort study. Included in this protocol is the detailed analysis of defocus profiles. This thesis investigates polynomial curve fitting to establish the most suitable curve and curve fitting method for use in future analysis of MIOLs with detailed defocus metrics. Defocus curves can highlight the differences in optical performance in MIOLs of differing addition powers, however, to add further complexity, previous literature has highlighted that addition power can vary individual to individual based on their ocular anatomy. Thus, investigation of an easily accessible clinical method to predict the likely achieved addition power post-implantation was performed.

A randomised intra-patient contralateral eye study assessed refractive outcomes and rotational stability in TIOLs. In addition, the performance of the corresponding manufacturer's calculators was evaluated in regard to refractive predictability and appropriate TIOL selection.

This thesis highlights the clinical features of modern MIOL and TIOL designs, demonstrating both the benefits and challenges incurred following implantation.

Contents

List of Abbreviations

ACA	Anterior corneal astigmatism
ACD	Anterior Chamber Depth
AIC	Akaike Information Criterion
AL	Axial length
ALP	Actual lens position
ANOVA	Analysis of Variance
AoF	Area of focus
ATR	Against the rule
BSS	Balanced saline solution
BVD	Back vertex distance
CCI	Clear corneal Incision
CDVA	Corrected distance visual acuity
CI	Correction index
CPS	Critical print size
CS	Contrast sensitivity
D	Dioptre
DC	Dioptre cylinder
DCIVA	Distance corrected intermediate visual acuity
DoF	Depth of focus
DS	Dioptre sphere
DCNVA	Distance corrected near visual acuity
ECCE	Extracapsular cataract extraction
EDoF	Extended depth of focus
ELP	Effective Lens position
HOA	Higher Order Aberration
K	Keratometry value
ICCE	Intracapsular cataract extraction
IOL	Intraocular lens
J_0	cylindrical effect at 180°
J_{45}	cylindrical effect at 45°
LOA	Limits of agreement
MIOL	Multifocal intraocular lens
MSE	Manifest spherical equivalent
MRI	Magnetic resonance imaging
MRS	Maximum reading speed
NAVQ	Near Acuity Visual Questionnaire
NHS	National Health Service
OCT	Optical coherence tomography
OLCR	Optical low coherence reflectometry
OVD	Ophthalmic viscoelastic device
PCA	Posterior corneal astigmatism
PCO	Posterior capsular opacification
RI	Refractive Index
QoV	Quality of vision
ROF	Range of Focus
SIA	Surgically induced astigmatism
TCA	Total corneal astigmatism
TIA	Target induced astigmatism
TIOL	Toric IOL
UDVA	Unaided distance visual acuity
UNVA	Unaided near visual acuity
VA	Visual acuity
V1	Visit 1
V2	Visit 2
WPM	Words per minute
WTR	With the rule

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Preface

This thesis comprising of seven chapters explores the clinical outcomes of multifocal and toric intraocular lenses.

Chapter One introduces the subject of cataract surgery and outlines the research aims. It provides a review of the current literature surrounding multifocal and toric intraocular lenses.

Chapter Two explores the most appropriate method of curve fitting for multifocal intraocular lenses to allow standardised analysis of defocus profiles. A study based on this chapter has been submitted to the Journal of Cataract and Refractive Surgery and is currently under review.

Chapter Three uses the curve fitting method established in Chapter Two, to calculate the addition power at the spectacle place achieved after implantation of multifocal intraocular lens. This chapter establishes a clinical method of predicting the post-operative outcome. A study based on this chapter has been submitted to the Journal of Refractive Surgery and is currently under review.

Chapter Four reports the clinical results and patient report outcomes of a randomised control trial comparing a monofocal and a multifocal intraocular lens. In addition, it details a proposed methodology for use in future studies to ensure robust evaluation and enable comparison of outcomes between studies. This study has been published in Journal of Cataract and Refractive Surgery 2020.

Chapter Five uses the robust methodology of Chapter Four to compare a cohort implanted with either a trifocal or an extended depth of focus intraocular lens. A study based on this chapter has been submitted to the Journal of Refractive Surgery and is currently under review

Chapter Six, the final experimental chapter, documents the results of an intra-patient randomised control trial exploring refractive outcomes and rotational stability of two toric intraocular lenses. A study based on this chapter has been submitted to the Journal of Refractive Surgery and is currently under review

Chapter Seven provides a summary and conclusions. It also outlines futures research objectives

Chapter One

Literature Review

1.1 Introduction

Globally, 10.8 million people are categorised as blind (severely sight impaired) and 35.1 million are classed as partially sighted (sight impaired) due to cataracts (Khairallah et al., 2015). In the developing world, many people are unable to have surgery for cataracts due to lack of services and/or clinicians (Aboobaker and Courtright, 2016, Khanna et al., 2011, Rao et al., 2011). In developed countries cataract surgery is one of the most commonly performed hospital procedures. Approximately 400,000 procedures are carried out each year in the UK alone and this is envisaged to continue to rise in view of its ageing population (Minassian, 2014). During cataract surgery, the natural crystalline lens is removed and an artificial intraocular lens (IOL) is implanted. This IOL is required to restore visual function. With greater accessibility to cataract surgery there has been a commensurate increase in patient expectations. In addition to the relative ease of surgery and its wide availability, there have been many developments to IOL design and calculation of IOL power since the first IOL was implanted by Sir Harold Ridley (Ridley, 1952). These advancements include correction of astigmatic and presbyopic refractive errors by way of toric intraocular lenses (TIOLs) and multifocal intraocular lenses (MIOLs).

A plethora of intraocular lens types are available, enabling patients to seek more than basic visual restoration following surgery (Tielsch et al., 1995). They may expect solutions to reduce or eliminate their dependence on spectacles even prior to the onset of cataract (Wilkins et al.,

2009). Such expectations require exceptional accuracy in IOL power calculation and a sound understanding of IOL design and functionality, to best suit a patient's visual requirements.

Despite the many advances over the years, there remain inaccuracies in IOL power calculations, particularly in TIOLs, that requires further exploration (Ferreira et al., 2017a, Norrby, 2008, Ribeiro et al., 2019). In addition, although distance visual outcomes are predictable in MIOLs, there is currently insufficient research to predict the effective near power of an MIOL at the spectacle plane achieved post-operatively.

Clinical outcomes on MIOLs are widely published, yet there is a lack of consistency in the methods utilised and often studies inadvertently bias toward one IOL design over another. These variations in methodology, can significantly reduce meaningful comparison of published literature, and as such, clinicians may not be adequately informed of the functionality of a particular MIOL.

1.2 Anterior Segment Anatomy

The anterior segment refers to the anterior 1/3 of the eye, and is comprised of the structures anterior to the vitreous cavity, including the cornea, iris and crystalline lens (Snell, 1998). It is comprised of two chambers; the anterior chamber, the cavity from the cornea to the anterior iris surface, and the posterior chamber, which is the cavity from the posterior iris surface to the anterior vitreous face (Figure 1.1).

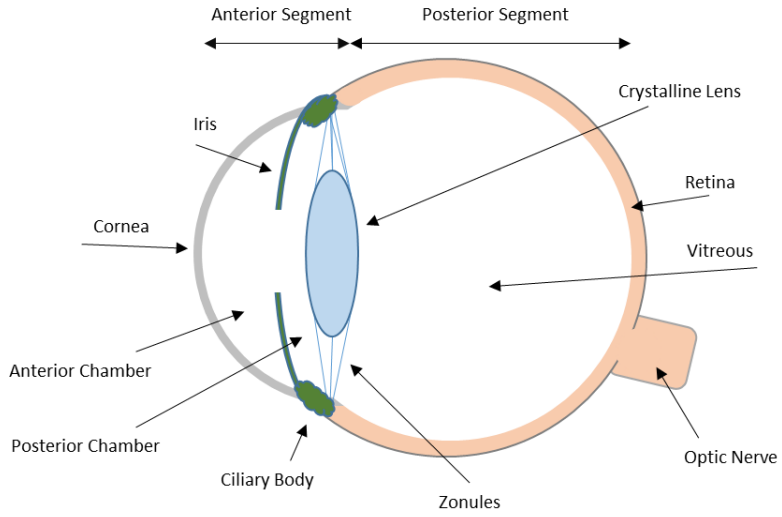


Figure 1.1: Basic Eye Anatomy

Both chambers are filled with aqueous humour, a clear fluid that is secreted by the ciliary body. The aqueous humour provides nutrients to the avascular structures of the anterior segment and maintains the intraocular pressure of the globe. (Snell, 1998). The zonules are fibrous strands connecting the ciliary body to the crystalline lens, inserting close to the lens equator (Kaufman, 2010). They act as suspensory ligaments. Both the cornea and crystalline lens are responsible for the refractive power of the eye and thus will be discussed in more detail.

1.2.1 Cornea

The cornea is an avascular transparent structure, approximately 550µ thick centrally, with thickness increasing towards the periphery (DelMonte and Kim, 2011). It comprises 5 layers; epithelium, Bowman's membrane, stroma, Descemet's membrane and the endothelium. However in recent years, a 6th layer has also been introduced in the literature (Dua et al., 2013). The cornea has an anterior diameter of approximately 11.5 to 12mm horizontally, but only 10.5 to 11mm vertically, whereas its posterior surface has a diameter of 11.5 to 12mm in both meridians (Rufer et al., 2005). The cornea is responsible for 2/3 of the eyes refractive power,

approximately 42 dioptres (D) (Lens, 1999, Snell, 1998). Medical terms relating to the cornea often start with the prefix “kera” from the Greek word κερας for horn.

1.2.1.1 Corneal Epithelium

The corneal epithelium is the anterior most layer of the cornea, comprised of 5-7 layers of cells. Corneal epithelial cells are regenerated regularly. They follow an orderly apoptosis (planned cell death), with deeper cells replacing the superficial layers, resulting in complete epithelial turnover in 7-10days (Hanna et al., 1961). It is a thin layer (40-50µ). It acts as a barrier to protect the underlying cornea from the invasion of potentially infectious material. The epithelium is coated with the tear film and this is important for the optical function of the eye (DelMonte and Kim, 2011).

1.2.1.2 Bowman’s Layer

Bowman’s layer is an acellular layer of collagen fibres, protecting the corneal stroma. It is only approximately 15µ thick (Merindano et al., 1997).

1.2.1.3 Stroma

The stroma accounts for 80-85% of the corneal thickness. It is a precisely arranged matrix of collagen fibres. This highly regular arrangement contributes towards the mechanical strength and the transparency of the cornea (Jester et al., 1999). The stroma also contains keratocytes, specialised fibroblasts that function to repair the cornea following injury (DelMonte and Kim,

2011). In the event of corneal injury, these keratocytes are activated and migrate to the site of injury (Stramer et al., 2003).

1.2.1.4 Descemet's Membrane

Descemet's membrane is a thin acellular layer, comprised mainly of collagen that acts as a basement membrane attaching the corneal endothelium to the stroma (Johnson et al., 1982).

1.2.1.5 Corneal Endothelium

The endothelium is the posterior layer of the cornea. It is a single layer with a honeycomb style arrangement of mitochondria rich cells only approximately 5µ thick. The density of cells decreases throughout life (Bahn et al., 1986). The endothelium's function is two-fold; it allows nutrients from the aqueous humour to pass to the superficial layers of the cornea, yet also draws water osmotically from the stroma into the aqueous. It is vital to corneal transparency by maintaining the deturgescence (relative dehydration) of the stroma (Bourne, 2003). Unlike the epithelium these cells do not regenerate, yet they are capable of polymegathism (variability of size) and polymorphism (variability of shape), ensuring that as cells die, the adjacent cells alter in size and shape (Lens, 1999). If the endothelial cell count falls below a threshold level, then corneal transparency is reduced due to failure to maintain deturgescence (Bourne, 2003).

1.2.1.6 Dua's Layer

In recent years, a sixth layer (Dua's layer) has been proposed (Dua et al., 2013). This layer is located between the stroma and Descemet's membrane, yet it has been disputed by other

authors as pre-Descemet's stromal tissue that has previously been described in surgical dissection accounts (Jafarinasab et al., 2010, Jester et al., 2013, McKee et al., 2014).

1.2.1.7 Corneal Nerves

The cornea is innervated by the ophthalmic division of the V^{th} cranial nerve (trigeminal). The stromal nerves originate from the sclera and enter the stroma radially. Some stromal nerves connect at the centre, however most penetrate upwards into the central epithelium. The peripheral epithelium is innervated by the superficial limbal network (He et al., 2010).

1.2.2 Crystalline Lens

In addition to the refractive properties of the cornea, the crystalline lens provides approximately 1/3 of the eye's dioptric power (Snell, 1998).

The crystalline lens is a transparent biconvex structure situated posterior to the iris and anterior to the vitreous body (**Figure 1.1**). It is suspended in position by the zonules, these suspensory ligaments connect the lens to the ciliary body.

In an adult, the lens measures approximately 10mm in diameter and is approximately 4mm thick (Snell, 1998). The lens is made up of 3 main parts; lens capsule, lens epithelium and lens fibres. In medical terms, an eye with a crystalline lens is referred to as phakic.

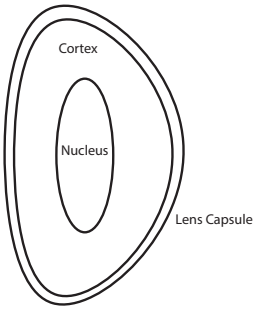


Figure 1.2: Anatomy of crystalline lens

1.2.2.1 Lens Capsule

The lens capsule is the outermost layer of the lens. It is an elastic basement membrane encircling the lens. The capsule is composed mainly of Type IV collagen and glycosaminoglycans (Forrester, 1996). The elasticity of the capsule allows the lens to alter shape (reduces both anterior and posterior radius of curvature) when not under the tension of the zonular fibres as described in Helmholtz's theory of accommodation (Hartridge, 1925). The posterior lens capsule is thinner than the anterior lens capsule as it does not continue to increase in thickness through life, as the anterior capsule does (Fisher and Pettet, 1972, Seland, 1974).

1.2.2.2 Lens Epithelium

The lens epithelium is a simple cuboidal epithelium (Forrester, 1996). The function of the epithelium is twofold. Cells located near the equator actively divide and differentiate into lens fibres. The remaining epithelial cells transport ions and nutrients from the aqueous humour to

the lens interior and export ions and capsular secretions, thus regulating the homeostatic functions of the lens and maintaining osmotic concentration (Candia, 2004).

1.2.2.3 Lens Fibres

The main mass of the lens consists of lens fibres, which run meridionally from the posterior to the anterior lens surface and are U-shaped. The earliest formed fibres are found in the central nucleus of the lens and secondary fibres are added to the outer layers progressively, thus the superficial fibres forming the outer cortex of the lens are the most recently generated (**Figure 1.2**). As such, the lens continues to grow throughout life increasing in mass and weight (Glasser and Campbell, 1999). During development of lens fibres, the cells lose their nuclei and become specialised for the production of lens proteins known as crystallins that constitute 60% of lens fibre mass (Bayramlar et al., 2017). Crystallins are water-soluble proteins that form high molecular weight aggregates that pack tightly within the lens fibres thus increasing the refractive index (the ratio of the velocity of light in a vacuum to its velocity in a specified medium) over the lifetime of the lens.

1.3 Refractive Function of the Eye

Refractive errors refer primarily to distance vision and the eye's refractive state when viewing parallel light from a distance object. The crystalline lens in a young eye is able to change shape. Through this ability to change shape, the lens is able to change its dioptric power allowing the eye to focus on objects both at distance and near (Koretz et al., 1997). This ability is known as accommodation.

1.3.1 Accommodation

For many years, there has been some debate concerning the exact mechanism by which accommodation occurs but the prevailing theory is that proposed by Helmholtz: during accommodation, the ciliary body contracts which releases zonular fibre tension. Without zonular tension the crystalline lens mass moves anteriorly, the lens thickness increases and the radius of curvature of both the anterior and posterior surface reduces (Hartridge, 1925)(**Figure 1.3**). In *vivo* support of this theory was initially difficult, as visualisation of the peripheral lens and ciliary processes is hampered by the iris, however some unique cases of aniridia have provided support for Helmholtz's theory (Baikoff et al., 2004, Wilson, 1997). High-resolution magnetic resonance imaging (MRI) in normal eyes has allowed visualisation of the entire lens, ciliary body and ciliary muscle and provided further support for Helmholtz theory (Strenk et al., 1999, Strenk et al., 2004).

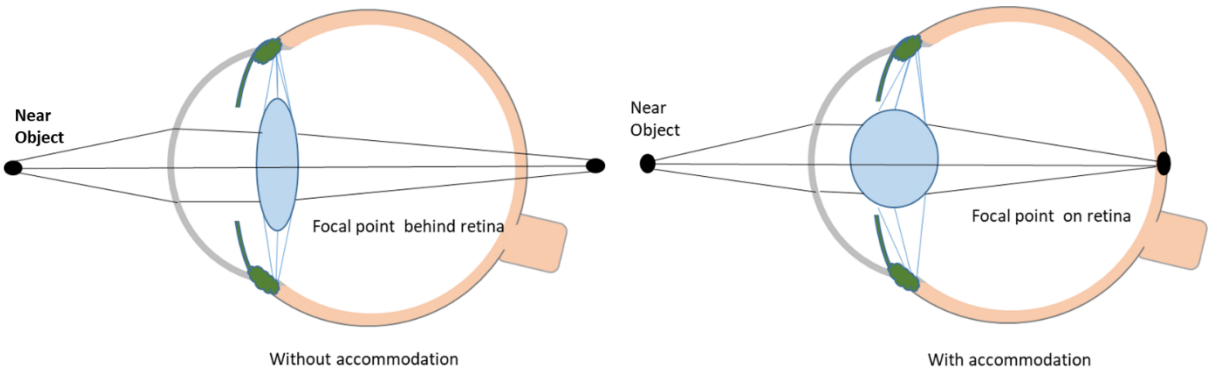


Figure 1.3: Accommodation

With accommodation, the dioptric power of the crystalline lens is increased. Thus, patients with a small hyperopic refractive error in distance viewing are able to accommodate, therefore increasing the dioptric power and focussing the rays on the retina, therefore negating the need

for spectacles. Accommodation is the mechanism by which near vision is achieved. When viewing a close object, the light rays incident on the cornea are divergent, thus increased refractive power is required to focus on the retina (Figure 1.3).

1.3.2 Presbyopia

The accommodative ability in all individuals decreases with advancing age (Glasser, 2008). This is known as presbyopia. The mechanism of which, has also been the subject of much debate. The loss of accommodation has been reported as multifactorial due to age-related changes involving all of the accommodative structures (Gilmartin, 1995, Koretz and Handelman, 1988, Weale, 1989). It was proposed that a loss in choroidal elasticity prevents the ciliary muscle returning to a relaxed state (Bito et al., 1982). However, MRI imaging has since shown that although this is correct for rhesus monkeys, the function of the ciliary muscle is maintained throughout life in humans (Strenk et al., 2004). However, there are configurational changes to the ciliary muscle with age (Strenk et al., 1999, Strenk et al., 2006, Tamm et al., 1992) yet, it appears that lenticular changes are almost wholly responsible for the loss of accommodation in presbyopia. The increase in lens thickness over time is the primary contributing factor in presbyopia (Glasser and Campbell, 1999, Glasser, 2008, Heys et al., 2004, Weeber et al., 2005, Weeber et al., 2007). Additionally, the lens grows in size and weight throughout life (Brown, 1976, Glasser and Campbell, 1999, Scammon, 1937, Strenk et al., 2004). This growth displaces the uveal tract anteriorly, rendering ciliary muscle contraction ineffective (Strenk et al., 2005). There is also an anterior shift in zonular insertion to the lens (Farnsworth and Shyne, 1979) and changes in thickness and elasticity of the lens capsule (Krag et al., 1997, Krag and Andreassen, 2003). As accommodative ability decreases with increasing age, near vision (reading) spectacles are then required to maintain near visual acuity.

1.4 Cataract

Loss of accommodation is not the only consequence of an aging lens. Light scattering and ocular aberrations increase with aging, ultimately resulting in a cataract (Alio et al., 2005, Fujikado et al., 2004). A cataract is described as opacification of the normally transparent crystalline lens. With advancing age, the lens proteins undergo a degenerative change resulting in a loss of transparency, thus senile cataracts are the most common type. However, cataracts can also be described as congenital, traumatic, toxic or secondary to systemic or ocular disease (Snell, 1998). Typically, cataracts are defined by their location and graded by the density of the opacification. The three most common types of cataracts are nuclear sclerotic, cortical and subcapsular.

1.4.1 Nuclear Sclerotic Cataract

As discussed above, the nuclear lens fibres continually grow throughout life and as they compress together they form a larger, denser and less pliable structure. The release of pigment by the lens proteins, reduces the transparency of the lens, causing the nucleus to have a yellow or brown appearance (Thompson and Lakhani, 2015)(**Figure 1.4**). Nuclear sclerosis is the most commonly occurring cataract and can cause a myopic shift in the patient's refractive error (Steinert, 2009). This myopic shift is the result of changes to the refractive index of the nucleus due to increase in density (Cho et al., 2013).

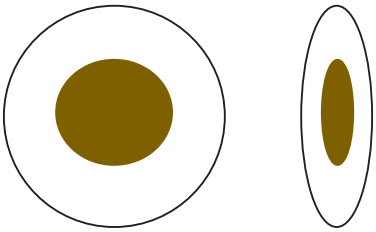


Figure 1.4: Front and profile diagram of a nuclear sclerotic cataract

1.4.2 Cortical Cataract

Cortical cataracts have a spoke-like appearance, where fluid clefts form in the cortex of the lens, displacing bordering cells (Snell, 1998) (Figure 1.5).

Figure 1.5: Front and profile diagram of a cortical cataract

If the peripheral spokes are outside the margins of the pupil, there is a lesser effect on visual acuity, hence the Beaver Dam Eye Study showed that the frequency of cataract surgery was less in patients with cortical cataracts (Klein et al., 1997).

1.4.3 Posterior Subcapsular Cataract

The proliferation of peripheral epithelial cells occurs in the lens; these cells collect at the back of the lens and form a plaque on the posterior surface (Snell, 1998). The formation of a

posterior subcapsular cataract can also be linked to steroid medications and trauma (Steinert, 2009). Patients with posterior subcapsular cataracts may report symptoms of glare and reduced vision disproportionate to measured levels of visual acuity (Stifter et al., 2004).

Figure 1.6: Front and profile diagram of a posterior subcapsular cataract

1.5 Cataract Surgery

Cataract surgery involves the removal of the natural crystalline lens. The main indications for cataract surgery are visual impairment and visual disturbance due to clouding of the natural lens (opacification). However, surgery can also be medically indicated due to conditions such as phacolytic or phacomorphic glaucoma (Kothari et al., 2013). Phacolytic glaucoma is the onset of acute open-angle glaucoma caused by lens proteins leaking from a mature or hypermature cataract through microscopic openings in the lens capsule. These proteins and inflammatory cells block the trabecular meshwork, thus elevating intraocular pressure (IOP) (Papaconstantinou et al., 2009). Phacomorphic glaucoma can present acutely as an angle closure glaucoma with an marked increase in IOP, characterized by pain, nausea and blurred vision or it can present as a chronic angle closure glaucoma asymptomatically (Papaconstantinou et al., 2009).

As the crystalline lens contributes 1/3 of the eyes refractive power, an eye without a lens (aphakic) would require a significant hyperopic spectacle prescription and would have very poor acuity without spectacles. It is preferable to replace it with an artificial lens of optical power (intraocular lens), thus the eye becomes pseudophakic (with artificial lens). The first intraocular lens (IOL) was implanted by Sir Harold Ridley in 1949 (Ridley, 1952).

Cataract surgery is also performed on patients before they develop cataracts. This involves removal of the clear (pre-cataractous) lens and this is commonly known as clear lens exchange or refractive lens exchange. In these cases, the purpose of the surgery is not to restore visual function that has been impaired due to lens opacification but to alter the refractive power of the eye. The natural crystalline lens is replaced with an IOL with the appropriate optical power calculated to eliminate or reduce refractive error/ spectacle dependence (Wilkins et al., 2009). Nowadays, like spectacles and contact lenses, IOLs are available to correct most of the refractive errors of the eye, namely spherical, astigmatic and presbyopic refractive errors. Monofocal IOLs are used to correct spherical refractive errors, typically for distance vision. Toric intraocular lenses (TIOLs) are used in the correction of astigmatic refractive errors (Ahmed et al., 2010, Visser et al., 2013) and accommodating, multifocal intraocular lenses or extended depth of focus (MIOLs) are often used to correct presbyopia (Breyer et al., 2017). IOL designs will be further discussed in Section 1.7 to 1.13. It is possible to calculate the required intraocular lens power using ocular biometry measurements. These will be further discussed in section 1.6.

1.5.1 Methods of cataract surgery

Cataract surgery dates back to the 5th century, where initial techniques were referred to as couching (Davis, 2016). A needle was introduced into the eye to dislocate the cataractous lens from the zonules, allowing it to fall back into the vitreous cavity, thus moving it out of the central line of vision. The eyes remained aphakic. However, post-operative complications such as retinal detachment and endophthalmitis have been reported (Davis, 2016). Surgery has significantly evolved throughout the centuries, yet there are reports that couching is still practiced in some developing countries (Isawumi et al., 2013).

This technique was then superseded by intracapsular cataract surgery and then by extracapsular cataract surgery which remains the most popular technique to date.

1.5.2 Intracapsular Cataract Extraction

Intracapsular cataract extraction (ICCE) involves removing both the entire crystalline lens (nucleus and cortex) and the outer lens capsule, often referred to as the capsular bag, by severing the zonular attachments. The entire lens is then removed through a large limbal (the junction between the cornea and sclera) incision usually 10.5 to 12.0mm (Mamalis, 2003).

1.5.3 Extracapsular Cataract Extraction

Improvements in cataract surgery, led to the advent of extracapsular cataract extraction (ECCE), where an opening is made in the anterior capsule, the lens cortex and nucleus is removed via the anterior capsular opening. In addition, ECCE has several advantages over ICCE including a smaller incision (5.5 to 7.0mm)(Mamalis, 2003). With the introduction of IOLs, it is possible to make a patient pseudophakic. IOLs require support in order to maintain position

and stability. With ECCE procedures, it is possible to implant an IOL in the remaining capsular bag. However, following an ICCE procedure or an ECCE procedure where there has been damage to the capsular bag, there is no such support. Therefore, often anterior chamber IOLs are used (Hennig et al., 2001, Nag et al., 2001). Alternatively, it is possible to use a posterior chamber IOL and the IOL can be fixed (sutured) to the sclera (Sindal et al., 2016).

1.5.4 Phacoemulsification with intraocular lens implantation

Phacoemulsification is a technique used in ECCE surgery, first advocated by Charles Kelman in 1967 (Kelman, 1967). It involves emulsification of the crystalline lens using a high frequency ultrasound probe, then irrigation and aspiration to remove the lens particles from the eye. It is the most commonly performed method of cataract extraction in the developed world (Feizi, 2011).

1.5.5 Anaesthesia

Cataract surgery can be performed under general anaesthesia, local anaesthesia or topical anaesthesia.

1.5.5.1 General Anaesthesia

General Anaesthesia is required for only a small percentage of patients undergoing cataract surgery, usually if the patient is unable to remain immobile for the duration or is unable to lie comfortably supine (Leaming, 2004).

1.5.5.2 Local Anaesthesia

There are three main anaesthetic procedures used to achieve local anaesthesia in cataract surgery: retrobulbar, peribulbar and sub-Tenon's block. Until the 1990's retrobulbar and peribulbar were the most commonly used anaesthetic techniques used in cataract surgery (Davis and Mandel, 1986, Hamilton, 1996).

Retrobulbar (intraconal) block is a form of regional anaesthesia for the globe. Local anaesthetic is injected into the intraconal space (the muscle cone formed by the 4 recti muscles) and thus, it then spreads to the motor and sensory nerves of the eye. It causes akinesia of the extraocular muscles (inability to voluntarily move the eye) and anaesthesia of the anterior and posterior chamber.

Peribulbar (extraconal) block achieves similar akinesia and anaesthesia as a retrobulbar block but deposits the anaesthetic outside of the muscle cone, is technically easier to place and the risk of penetration of the optic nerve is decreased (Fahmi and Bowman, 2008)(Figure 1.7).

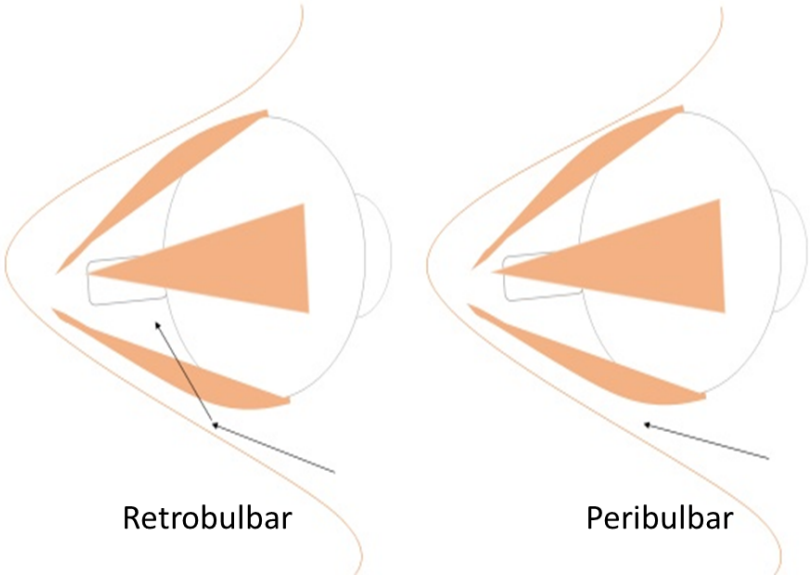


Figure 1.7: Local Anaesthesia injection sites

Both require a sharp needle to be introduced into the orbit and thus there is a risk of globe perforation or penetration of the optic nerve. These complications are rare (Edge and Navon, 1999, Nicoll et al., 1987) but serious thus, there has been a move towards less invasive methods.

Such a technique is a Sub-Tenon's block. Following dissection of the conjunctiva, using a blunt cannula, local anaesthetic is injected into the space between the sclera and Tenon's capsule (the fascial sheath of the eyeball), leading to analgesia and akinesia (impairment of voluntary movement) of the globe (Hosoda et al., 2016). As no sharp needle is used, perforation is less likely and has been reported to have fewer complications relative to a retrobulbar block (Eke and Thompson, 2007).

1.5.5.3 Topical anaesthesia

With advances in surgical techniques, smaller incisions and minimally invasive techniques such as phacoemulsification, total akinesia of the globe is no longer required in some cataract surgeries and as such, topical anaesthesia has increased in popularity.

Topical anaesthesia involves instilling anaesthetic eye drops on the ocular surface, thus anaesthetises the cornea and conjunctiva, but provides no akinesia. It can be used in patients who are co-operative and able to lie supine and motionless for the duration of surgery. It provides no akinesia of the extraocular muscles; thus, the surgeon must be able to tolerate some potential eye movements. A randomised trial, comparing retrobulbar anaesthesia to topical anaesthesia, found similar rates of intraoperative complications, and discomfort between the two groups and there was a significant patient preference for topical anaesthesia (Jacobi et al., 2000). Topical anaesthesia allows for rapid visual rehabilitation following surgery

(Friedman et al., 2001, Leaming, 2004) without the risks associated with retrobulbar or peribulbar anaesthesia (Nielsen, 1995).

A 2009 national study in the UK found that 95.5% of cataract surgery took place under local anaesthetic, with 46.9% being Sub-Tenons block and 33.3% topical anaesthetic alone (El-Hindy et al., 2009).

With any of the local or topical anaesthetic techniques, sedation can be used in addition. However, in the UK only 1.4% of cataract surgeries occurred under sedation (El-Hindy et al., 2009).

1.5.6 Surgical Technique

Phacoemulsification surgery requires a smaller incision than traditional ECCE techniques as the lens is emulsified before being aspirated and typically, surgeons adopt either a bimanual or a coaxial approach. In a bimanual technique, two corneal incisions are made and two hand pieces are used, one for irrigation and the other for aspiration/phacoemulsification.

Conversely, in a coaxial approach, a single hand piece provides irrigation, aspiration and phacoemulsification, allowing one corneal incision and a second small incision (limbal paracentesis) created at approximately three clock hours (90°) from the planned incision site when using a two handed approach.

1.5.6.1 Ophthalmic Viscosurgical Devices

Ophthalmic viscosurgical devices (OVDs) are viscoelastic substances which have essential roles in intraocular surgery (Liesegang, 1990). There are 2 groups of OVDs, cohesive and dispersive and both have a role in cataract surgery (Arshinoff and Jafari, 2005). Cohesive OVDs are high molecular weight, high viscosity substances, and as such are used to deepen/maintain space in the anterior chamber during cataract surgery. Dispersive OVDs are low viscosity, low molecular weight substances which can disperse within the anterior chamber to coat and protect the corneal endothelium during surgery (Arshinoff and Jafari, 2005, Lane and Lindstrom, 1992).

1.5.6.2 Incision

There are two principle types of wound incisions used in modern cataract surgery, the scleral tunnel and the clear corneal incision (Figure 1.8).

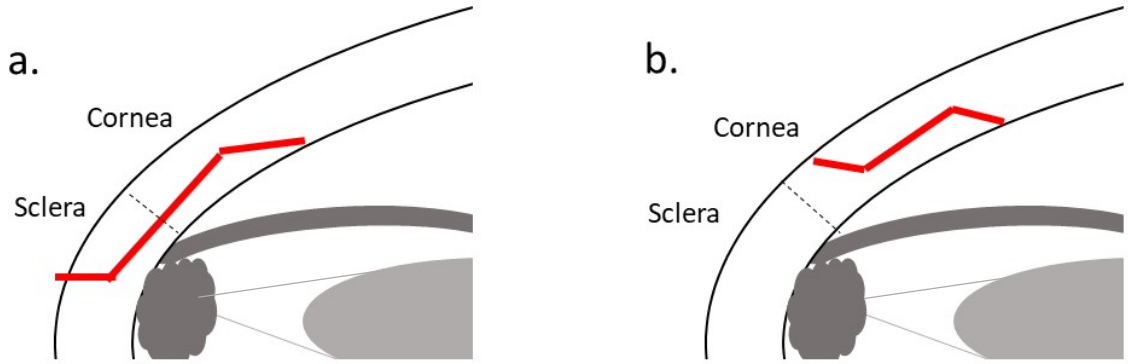


Figure 1.8: a. Diagram of scleral tunnel incision b. Diagram of clear corneal incision

Clear corneal incisions are reported to be the most commonly performed incision (Leaming, 2004) and as such will be described here. Corneal incision widths are determined by the size

of surgical instruments and type of IOL. As technology has advanced, the development of smaller probes and intraocular lens injectors has led to incisions reducing in size. Incisions as small as 0.9mm have been used for phacoemulsification, however this is not common (Agarwal et al., 2001). Presently the common incision size varies between 2.00 and 3.20mm and are typically governed by the size of the injector required to insert the foldable IOL of choice (Espiritu and Bernardo, 2009, Haldipurkar et al., 2020, Mencucci et al., 2019). The tri-planar architecture as seen in Figure 1.8 above, ensure that incisions typically do not require sutures and will self-heal (Linebarger et al., 1999).

The location of the corneal incision are typically dictated by co-existing ocular conditions, corneal astigmatism and/or ergonomic comfort of the surgeon. The effect of corneal incisions on corneal astigmatism, will be further discussed in Section 1.6.6.

Following the paracentesis, incision and injection of OVD, the next step is to create a continuous curvilinear, circular capsulorrhexis in the anterior capsule using a needle, forceps or femtosecond laser (Gimbel and Neuhann, 1990, Gimbel and Neuhann, 1991).

1.5.6.3 Capsulorrhexis

Following the paracentesis, incision and injection of OVD, the next step is to create a continuous circumlinear capsulorrhexis in the anterior capsule using a needle, forceps or femtosecond laser (Gimbel and Neuhann, 1990, Gimbel and Neuhann, 1991).

Creation of a capsulorrhexis is a key stage in extracapsular cataract surgery. It involves making a window in the anterior capsule. Early capsulorrhexis techniques were based on an incisional method that left irregular edges, which could potentially tear outwards and continue to the posterior capsule, often referred to as the can opener technique (Sharma et al., 2019).

Continuous circumlinear circular capsulorrhexis is the standard method, whereby starting from single puncture of the anterior capsule, it is torn in a continuous circular motion (Mohammadpour et al., 2012). With a continuous circular capsulorrhexis the capsule is less likely to be pulled out of centration and there is less likelihood of posterior capsular tearing (Gimbel and Neuhann, 1991). A capsulorrhexis ensures that an IOL implanted in the capsular bag should remain in the capsular bag as the forces of the capsulotomy are evenly distributed as the capsule contracts (Gimbel and Neuhann, 1991).

With the introduction of femtosecond laser assisted cataract surgery, an anterior capsulotomy can now be performed rather than a manual capsulorrhexis. When compared, laser capsultomies were closer to perfect circularity than manual capsulorrhexis (Schultz et al., 2015). In addition, greater repeatability and precision of size and centration has been shown with the femtosecond laser (Ali et al., 2017). Okada (Okada et al., 2014) found that variations in the size of manual capsulorrhexis can result in aberrant IOL positions, yet there is no conclusive evidence that refractive outcomes are better with femtosecond laser assisted cataract surgery (Day et al., 2016).

No differences in the fibrotic response of the capsule have been shown despite the differing techniques (Wertheimer et al., 2018).

1.5.6.4 Lens Dissection

Hydrodissection and hydrodelineation are techniques that use fluid to aid separation of structures. During hydrodissection, fluid is injected between the capsule and the nucleus, it mobilises the nucleus and separates it from the cortex (Fine, 1992). Balanced salt solution is used to free the adhesions between the capsular bag and the cortex of the lens to allow it to

move freely within the capsular bag. Hydrodelineation separates the harder central nucleus (endonucleus) from the softer outer epinucleus. Subsequently the free epinucleus acts as a protective cushion over the posterior capsule and the nucleus can be rotated freely and disassembled. This is less likely to cause stress on the posterior capsule or the zonules (Fine, 1992, Gimbel and Neuhann, 1990).

In order to disassemble the nucleus, various techniques using a phacoemulsification tip can be utilised. The phacoemulsification tip has a titanium or steel needle. The high frequency ultrasonic vibrations of the needle can sculpt and emulsify the nucleus. The fundamental principle is to emulsify the lens into smaller fragments to allow aspiration through the tip of the probe. A fine instrument, “chopper”, can be introduced through the paracentesis to aid with breaking down the nucleus into smaller pieces to aid emulsification. This step is typically performed in the posterior chamber, however, in the event of a posterior capsular tear, the nucleus can be prolapsed into the anterior chamber; this increases the risk of corneal endothelial damage (Gimbel, 1991). Gimbel was the first to describe a structured approach to disassembly of the nucleus and many fracturing and chopping techniques have since been described (Fine, 1991, Gimbel, 1992b, Gimbel, 1992a, Gimbel and Chin, 1995, Koch and Katzen, 1994, Vanathi et al., 2001). Regardless of technique, continual fluid flow through the eye is required to dissipate the heat created by the phacoemulsification probe and remove the emulsified nucleus, residual cortical material and OVD. Flow of fluid must be controlled to maintain the anterior chamber and this is controlled by varying the height of the fluid infusion bottle and adjusting the aspiration flow rate and vacuum settings.

1.5.6.5 Irrigation and Aspiration

After nuclear disassembly and phacoemulsification, cortical material remains and irrigation/aspiration is used to ensure all remnants are removed. Further viscoelastic material is introduced to maintain the depth of the anterior chamber, reform the capsular bag and to assist in IOL insertion.

1.5.6.6 Intraocular Lens Implantation

Unlike early rigid IOL designs, modern IOLs are foldable and injectable, thus can be introduced through a small incision. Further details on IOL design are discussed in section 1.7. In coaxial surgery, they are implanted through the main incision. In bimanual techniques, either of the incisions may be enlarged to facilitate the IOL injector, or a third incision can be made.

IOLs are either pre-loaded by the manufacturer or loaded at the time of surgery into an injector. The preservation of the capsular bag allows the IOL to be inserted in the bag, and unfolded for ideal positioning. Remaining OVD must be irrigated and aspirated from the eye to prevent subsequent intraocular pressure rises (Barron et al., 1985).

Finally, Prophylactic intracameral antibiotics are used to reduce the risk of endophthalmitis, a rare but sight threatening complication. This can be peribulbar, subconjunctival or intracameral. Intracameral antibiotics are now the commonest (Garcia-Saenz et al., 2010) and intracameral cefuroxamine has shown a fivefold decrease in post-operative endophthalmitis (Endophthalmitis Study Group and Refractive, 2007). Most small corneal incisions are self-sealing but must still be checked for leakage.

1.5.7 Femtosecond Laser Assisted Cataract Surgery (FLACS)

The studies included in this thesis, involve subjects who have had a standard coaxial phacoemulsification technique, previously detailed. However, in the last decade femtosecond laser technology has also become commercially available to assist with cataract surgery, and is capable of performing corneal incisions, anterior capsulotomy and lens fragmentation, thus it can be used in conjunction with phacoemulsification to perform cataract surgery. The literature suggests that despite the precision the laser adds, there is clinical equipoise between FLACS and conventional phacoemulsification techniques (Roberts et al., 2020). In addition, traditional phacoemulsification is currently more cost-effective (Bartlett and Miller, 2016).

1.6 Intraocular Lens Calculation

A good visual outcome after cataract surgery is largely dependent on the correct choice of IOL power for implantation. As the IOL is replacing the natural crystalline lens, there is an opportunity to control the refractive outcome. Sir Harold Ridley's pioneering IOL surgery, was successful in implanting a posterior chamber lens anatomically, unfortunately the refractive outcome was less that desirable (Apple and Sims, 1996). Ridley's initial design was based on the anatomical features of the crystalline lens, yet he failed to consider the differences in refractive index (RI) between his artificial implant made from PMMA (polymethylmethacrylate) and the RI of the natural lens. This resulted in a highly myopic outcome (Apple and Sims, 1996). Subsequent procedures with adjusted refractive powers were increasingly successful at restoring visual function, with markedly less refractive error, yet it was almost 20 years later before Fydorov published a method of estimating the required IOL to target emmetropia (Federov, 1967).

As cataract surgery is now also considered a refractive procedure, accurate correction of refractive error is fundamental in achieving a good visual outcome and reducing spectacle dependency post-operatively (Olsen, 1996). In order to calculate the required IOL power, we rely on both the accuracy of pre-operative anatomical measurements (ocular biometry) and the accuracy of intraocular lens calculation formulae (Drexler et al., 1998, Norrby, 2008).

1.6.1 Ocular Biometry

Ocular biometry is a non-invasive method of measuring anatomical features of the eye. It is used primarily in planning for cataract surgery and involves the measurement of various parameters of the eye. These include axial length (AL) and corneal power (K) in every instance but also others, such as; anterior chamber depth, white-to-white corneal diameter (WTW) and lens thickness (LT) depending on the device used (Figure 1.9). In early, IOL calculations, axial length and anterior chamber depth was measured by A-scan ultrasonography and corneal power by a keratometer.

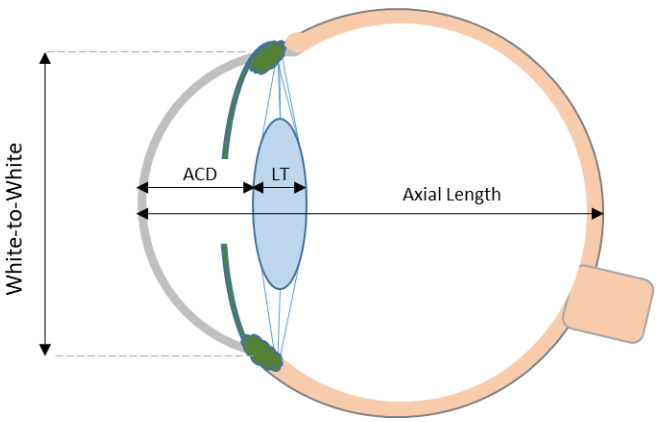


Figure 1.9: Biometry parameters

With the advent of optical biometers, using partial coherence interferometry (PCI) or optical low coherence reflectometry (OLCR) it was possible to use a single non-contact device to take all necessary measurements. The IOL master (Carl Zeiss Meditec, Germany) uses PCI and a dual-beam configuration, powered by a multi-mode laser diode to measure axial length (Drexler et al., 1998). The LenStar (Haag-Streit AG, Koeniz, Switzerland), is a device utilising OLCR and is powered with a super luminescent diode allowing measurement of all reflective structures in the eye, thus measuring AL, LT, ACD, corneal and retinal thickness. (Buckhurst et al., 2009, Holzer et al., 2009, Hui and Yi, 2014). Both devices have been found to be comparable (Buckhurst et al., 2009). Both the LenStar and IOL master use automated keratometry to measure corneal curvature. In addition both incorporate image analysis for measurement of white to white. There are many other optical biometers now available also based on PCI or OLCR, some of which incorporate features such as corneal topography and swept-source optical coherence tomography (OCT). These new models include the IOL Master 700 (Carl Zeiss Meditec, Germany) which also uses OCT to measure parameters.

1.6.1.1 Axial Length

The axial length (AL) of the eye is the distance from the corneal surface to the retina. Initially, axial length was only measured by immersion or applanation A-scan ultrasonography. In the immersion technique, a coupling fluid is used, whereas in applanation ultrasonography, the probe is in direct contact with the cornea. This can lead to corneal indentation and shortening of the axial length (Olsen and Nielsen, 1989). At this time, AL was found to be the most critical measurement for accurate IOL calculation, as it attributed to >50% of errors (Olsen, 1992). However, the introduction of optical biometry by partial coherence interferometry (PCI) has improved the standard and repeatability of AL measurements and other pre-operative

measurements (Drexler et al., 1998, Findl et al., 2001, Haigis, 2001). Measurements of AL taken by optical biometry are found to be longer than by ultrasound, this may be due to indentation of the cornea, or due to the slight variations in measuring points (Drexler et al., 1998, Haigis et al., 2000, Nemeth et al., 2003). The optical method (refractive axial length) measures from the tear film to the retinal pigment epithelium, while A-scan ultrasound (anatomical axial length) measures from the corneal surface to the vitreo-retinal interface (Nemeth et al., 2003). A-scan ultrasound is also limited by resolution (Norrby, 2008). Despite the advantages with optical biometry, A-scan ultrasonography still has a place in biometry, as it is still possible to obtain measurements in eyes with vitreous haemorrhage, corneal opacities or dense cataracts, which can be problematic for optical biometers (Lee et al., 2008, Nemeth et al., 2003).

1.6.1.2 Corneal Power

Corneal power can be measured by manual or automated keratometry, corneal tomography, scheimpflug imaging and OCT. Optical biometers incorporate automated keratometry. No method directly measures corneal power, however it is calculated from the corneal radii that can be measured from the reflected corneal surface. Currently only anterior corneal radius is measured, and an assumption used for the posterior corneal curvature based on a fixed ratio of anterior: posterior. However, some studies (Kirgiz et al., 2017, Saad et al., 2013) have shown that outcomes were improved when both anterior and posterior curvature were measured and therefore total corneal power considered, yet other studies found no improvement (Chan et al., 2017, Savini et al., 2017). In addition consideration must also be given to patients who have previously undergone laser refractive surgery, as they will no longer have a conventional anterior:posterior ratio and as such measurement of total corneal power is desirable (Tang et al., 2006)

1.6.1.3 Anterior Chamber Depth

Anatomically, the anterior chamber depth (ACD) is defined as the distance from the posterior surface of the cornea to the anterior surface of the crystalline lens along the optical axis (Barrett and McGraw, 1998). It must be noted though, that when considered in the context of IOL calculation it is measured from the anterior surface of the cornea, thus including corneal thickness (Olsen, 2007). It can also be measured by either A-scan ultrasound or optical biometry. ACD measured by ultrasound requires an anaesthetised cornea and a dilated pupil. As with AL, there can be an indentation of the cornea during measurement, thus shallowing the anterior chamber. A-scan ultrasound typically finds lower ACD values than optical biometry (Barrett and McGraw, 1998, Nemeth et al., 2003).

1.6.1.4 Effective Lens Position

Effective lens position is the expected post-operative position of the IOL. It is sometimes referred to as the pseudophakic ACD. Different IOL formula use different methods of estimating ELP based on a variety of pre-operative measurements, which may include AL, pre-operative ACD, K, LT, corneal height, age and refraction (Olsen, 2007). In fact, prediction of effective lens position (ELP), is now known to be the largest source of error (Norrby, 2008).

1.6.1.5 Lens Thickness

Lens thickness (LT) is measured from the anterior lens surface to the posterior lens surface. It can be measured by either ultrasound, OCT or OLCR. Greater variability has been shown with ultrasound techniques than OLCR (Buckhurst et al., 2009). LT measured with ultrasound typically results in a larger lens thickness (Savini et al., 2018a).

1.6.1.6 White-to-white

White-to-white is the horizontal corneal diameter. It is measured in millimetres via image analysis. It is routinely measured in biometry practices and has been used for haptic size calculation should an anterior chamber or angle-supported IOL be required (Gharaee et al., 2014) or for sizing of a phakic IOL (Lovisolo and Reinstein, 2005). However, there is controversy regarding the correlation of white-to-white measurement and sulcus diameter (Werner et al., 2004, Pop et al., 2001, Reinstein et al., 2009) and also there is no agreement in the literature regarding the relationship between white-to-white diameter and lens diameter (Dong and Joo, 2001, Khng and Osher, 2008, Vass et al., 1999). It is also used in some IOL formulae (Hoffer, 2000).

For all subjects undergoing biometry throughout this thesis, the LenStar optical biometer, which used optical low coherence reflectometry (Haag-Streit AG, Koeniz, Switzerland) was used.

1.6.2 Theoretical IOL Formulae

Fydorov first proposed a formula to calculate desired IOL power in 1967(Federov, 1967). These early theoretical formulae used thin lens vergence calculations to estimate the power of an IOL (Binkhorst, 1976, Colenbrander, 1973, Federov, 1967, Fyodorov et al., 1975). These formulae were all based upon **Equation 1.1** (Olsen, 2007) and require information on the AL, K, ELP, and the refractive index of the anterior(n_1) and posterior segment(n_2). Since ELP cannot be

measured pre-operatively, for the first generation formulae it was given an arbitrary value (Olsen et al., 1995).

$$IOL\ Power\ = \frac{n_2}{AL - ELP} - \frac{1}{\frac{1}{K} - \frac{ELP}{n_1}}$$

AL = axial length
ELP = Effective lens position
K = Corneal Power
n_1 = refractive index of anterior segment
n_2 = refractive index of posterior segment

Equation 1.1: Early Theoretic IOL formula

In the late 1970's, Binkhorst (Binkhorst, 1976) suggested, the constant pseudophakic ACD or ELP be replaced by an ELP prediction based on AL and many other formulae followed suit, using various methods to adjust predicted ACD (Emery, 1978, Holladay et al., 1988, Hoffer, 1984, Shammas, 1982). This resulted in a reduction of the errors (Olsen, 1992).

1.6.3 Regression based IOL Formulae

Further advancement in calculation came with regression derived formulae, such as SRK I and SRK II, developed by Sanders, Retzlaff and Kraff, where correction factors (regression coefficients) were used to refine the calculations and improve accuracy (Retzlaff, 1980a, Retzlaff, 1980b, Sanders and Kraff, 1980). The constants used in such formula are theoretical values, in the SRK formulae they are referred to as *A-constants*, and link the lens power to AL and K. They are empirically derived based on post-operative results that are specific to IOL

design. However, they were best suited to the datasets that they were derived from, hence the use of a different device for AL or K measurement could result in inaccuracies. This meant the *A-constant* required continual refinement and personalisation depending on the IOL design, device and surgeon.

1.6.4 Modern IOL formulae

Third generation formulae use a combination of theoretical and regression based calculations to optimise outcomes (Olsen, 2007). The number of parameters assessed varies from 2 up to 7 depending on the formula (Kane et al., 2016). Algorithms based on using both AL and K have been established to improve prediction of ELP (Haigis, 2004, Holladay et al., 1988, Olsen et al., 1990, Olsen et al., 1992, Olsen et al., 1995, Sanders et al., 1990).

1.6.4.1 Two parameter formulae

The Holladay, SRK/T and Hoffer Q formulae, are two parameter formula, which are still used in clinical practice, all use slightly different method to achieve this. They also refer to their constants by different terms; Holladay uses *SF* (surgeon factor) (Holladay et al., 1988), SRK/t uses *A-constant* (Retzlaff et al., 1990) and Hoffer Q uses *pACD* (Hoffer, 1993). The Holladay formula calculates ELP from corneal height (endothelium to iris plane) based on Fyodorov's method (Federov, 1967, Fyodorov et al., 1975) using AL and K, plus corneal thickness and SF (Holladay et al., 1988). The Holladay and SRK/t also vary in the refractive index assumption for the cornea. The Hoffer Q calculates corneal height by a method establish by its authors (Hoffer, 1993).

1.6.4.2 Three parameter formulae

The Haigis formula utilises three parameters, pre-operative ACD measurements in addition to AL and K measures in its prediction of ELP (Haigis, 2004). It also uses three constants a_0, a_1 and a_2 that are derived to produce a mean zero prediction error. The first (a_0) is similar in its function to Holladay's *SF* or SRK/T's *A-constant*, the remaining two constants; a_1 and a_2 relate to ACD and AL respectively.

1.6.4.3 Multiple parameter formulae

In addition, formulae such as the Olsen formula use five parameters, AL, ACD, K, Lens thickness and pre-operative refraction having found that each of these factors had a significant effect on successful prediction of ELP (Olsen, 2006). Kane uses six parameters, AL, K, ACD, lens thickness, central corneal thickness and gender (Connell and Kane, 2019). Holladay II uses seven parameters, adding age and white-to-white to the above but omitting gender. The Barrett II universal formula uses a theoretical model eye to predict ACD from AL and K and has been shown to increase post-operative refraction accuracy compared to the previously discussed formulae in AL >22mm (Kane et al., 2016, Melles et al., 2018). In shorter eyes (AL <22mm), the relative inaccuracy of predicting post-operative refractive outcomes is well documented, often the Hoffer Q is considered the formula of choice in short eyes (Gavin and Hammond, 2008, Hoffer, 2000). However, the literature is equivocal, with other studies reporting improved accuracy with the Haigis formula (MacLaren et al., 2007, Roh et al., 2011, Wang et al., 2018), although perhaps only when ACD is < 2.40mm (Eom et al., 2014). Kane found in his comparative study that all 7 commonly used formulae performed equally well in short eyes (Kane et al., 2016).

1.6.5 Hill RBF

The Hill-RBF (radial basis function) method uses advanced data interpolation and pattern recognition to select IOL power. It is self-validating. Currently, if there are insufficient numbers of similar eyes already in the database, an out of bounds message is provided and the calculation not used. As the dataset increases such messages should become less likely. It is optimised for use with the biometry device LenStar (Haag-Streit AG, Koeniz, Switzerland) and not currently available on other platforms. The Hill RBF 1.0 was able to target emmetropia only but version 2.0 allows the choice of target spherical equivalent. When version 1.0 was compared to existing formulae, it was not found to be more accurate than the Barrett II Universal (Kane et al., 2017). However, when version 2.0 was assessed, the Hill-RBF outcomes were improved, thus it was non-inferior to the Barrett II universal, but no significant improvement in accuracy was noted (Connell and Kane, 2019).

1.6.6 Surgically Induced Astigmatism

IOL formulae calculate the spherical IOL power, but we must also consider astigmatic refractive errors. All cataract surgery requires an incision to be made to open the eye. Incisions to the cornea can alter the shape, and thus the toricity of the cornea. This change is referred to as Surgically Induced astigmatism (SIA). An incision will cause a flattening effect on the meridian it is placed (Hirnschall et al., 2014). Incisions less than 3mm produce astigmatic changes of <0.5D (Armeniades et al., 1990, Samuelson et al., 1991).

In order to improve patient outcomes, it may be desirable to make the incision on the steeper axis to relax (flatten) the tissue and thus reduce corneal astigmatism (Merriam et al., 2003, Tejedor and Murube, 2005). However, it is not always surgically or ergonomically possible to

do so, depending on the steepest meridian, in relation to the nose, and dependent on the dominant hand of the surgeon (Hashemi et al., 2016).

Previous studies have shown less SIA in temporal incisions compared to superior incision (Mallik et al., 2012, Oshika et al., 2000, Roman et al., 1998). Therefore, often surgeons use a temporal incision as their standard approach (Leaming, 2004, Pick et al., 2008).

In patients with small amounts of astigmatism, using an on axis or temporal incision may be sufficient to reduce existing astigmatism. However in patients with astigmatism > 1.50D, then astigmatic correction with a toric IOL (TIOL) should be considered.

1.6.7 Toric IOL calculations

When implanting a TIOL, the SIA must be taken into account in order to appropriately determine TIOL power (Hill and Potvin, 2008). Thus, specific toric calculators are used rather than the IOL formulae previously discussed. The power of the TIOL can be calculated using described methods or by the calculation programs provided by individual IOL manufacturers (Langenbucher et al., 2009). Due to the potential variability introduced by using these different modalities of calculations, there have recently been several studies exploring the efficacy of to TIOL calculators. (Koch et al., 2013, Ribeiro et al., 2019, Visser et al., 2013, Yang et al., 2019b, Yang et al., 2019a). Ribeiro stated that the main source of residual refractive errors after TIOL implantation was the methodological error in predicting the toricity of the TIOL required (Ferreira and Ribeiro, 2018). He found that the Barrett and PhysIOL calculators provided the least residual error, but that all methods provided lower residual prediction errors in against-the-rule (ATR) compared to with-the-rule (WTR) astigmatism (Ferreira and Ribeiro, 2018). Koch

investigated different devices for measuring corneal astigmatism and found that all overestimated astigmatism in WTR and underestimated in ATR (Koch et al., 2012).

Calculation of the cylindrical correction required can be subject to error. It requires precise consideration of corneal astigmatism. The cylindrical power corrected in the IOL plane has a corresponding magnitude of astigmatism corrected in the corneal plane and most toric calculators assume this to be a fixed ratio. However, variability exists due to the distance between the cornea and the IOL (Hayashi et al., 2010). A fixed ratio appears to result in under corrections in long eyes and overcorrections in short eyes (Shimizu et al., 1994). The addition of pachymetry and ACD has been found to overcome this limitation (Sun et al., 2000).

Most calculators only consider anterior corneal astigmatism, however, it has been suggested that posterior corneal astigmatism is the most important factor for post-operative refractive error (Savini and Naeser, 2015). In response to these limitations, new nomograms, formulas and calculators have been developed to adjust for posterior corneal astigmatism (Abulafia et al., 2016, Goggin et al., 2015, Koch et al., 2013).

A recent retrospective study, compared pre-operative calculations from a manufacturer's calculator with and without the Baylor Nomogram adjustment, Abulafia-Koch formula and Goggin coefficient (Ferreira et al., 2017a). It also compared the Barrett online calculator and ray tracing software. The Barrett calculator performed best overall as the mean absolute error in the predicted residual astigmatism was lowest (Ferreira et al., 2017a). Yang also found least prediction errors when using the Barrett calculator (Yang et al., 2019a, Yang et al., 2019b).

Due to the current debate regarding the influence of posterior corneal astigmatism, further investigation of current toric IOL calculation methods is required.

1.6.8 Presbyopic Calculations

IOL formulae are typically used to predict the IOL power required to achieve emmetropia but can also be used to target a specific refractive error, for example, some patients may wish to remain myopic post-operatively to allow near vision without spectacles.

IOL formulae have been shown to be predictable when using multifocal intraocular lenses, however to date, published literature only reviews the predicted distance result (Fernandez et al., 2019, Koch et al., 2017, Reitblat et al., 2015). There is little information on the expected near residual refraction following MIOL implantation. Manufacturers provide the addition power of an MIOL at the IOL plane, yet the clinically valuable metric is the addition power at the spectacle plane. The addition power at the spectacle plane, can be converted to a focal length, thus revealing the working distance at which an individual should achieve their best near visual acuity. The focal length is the mathematical reciprocal of the power. For example a +2.50 addition power at the spectacle plane, will give a near focal point at 40cm. This is important information for clinicians and patients, in order to choose a lens which is best suited to their lifestyle or work requirements. Previous studies suggest that the addition power achieved post-operatively (effective addition power) varies in individuals. This is dependent on their ocular anatomy (ocular biometry measurements) (Eom et al., 2017, Petermeier et al., 2009b, Savini et al., 2016).

Eom (Eom et al., 2017) investigated the relationship between ELP and addition power, they calculated effective addition power from defocus data and predicted ELP using Haigis's method. They found that a larger ELP resulted in a lower addition power at the spectacle plane. Their paper discussed their own calculator to calculate ELP prior to surgery but unfortunately this does not appear to be commercially available.

Petermeier (Petermeier et al., 2009b) demonstrated that hyperopes had a shorter near working distance than emmetropes when implanted with the same MIOL, and myopes had a longer near working distance than both.

Savini's study (Savini et al., 2016) was theoretical, they used the Hoffer Q, Holladay and SRK/T formula to calculate emmetropia in theoretical eyes with K ranging from 39 to 48D and AL ranging from 20-30mm. They calculated the spectacle plane addition power using this method for IOL plane addition and produced a set of tables for IOL plane addition powers of +2.50, +3.00 and +4.00. These tables highlight that the near focal point can vary depending on K and AL, as such with a +2.50 addition power, near focal point varied from 53-72cm. For +3.00D and +4.00D addition powers the variation was 44-60cm and 33-44cm respectively (Savini et al., 2015).

These tables could be useful to surgeons planning surgery, but are yet to be proven *in vivo*, and do not cater to all commercially available addition powers.

To date, there remains no simple clinical method for predicting the post-operative spectacle plane addition power of an MIOL, thus there remains an element of uncertainty in the near refractive outcome of these IOLs.

1.7 Intraocular Lenses

It took almost 40 years, after Ridley's first surgery, before lens implantation finally became widely accepted as an integral part of cataract surgery (Allan, 2000, Apple and Sims, 1996) . This was largely due to issues with IOL design and surgical techniques.

1.7.1 History of IOL Design

At their inception, IOLs were biconvex discs, made from PMMA that mimicked the characteristics of the crystalline lens. They were placed against the intact posterior capsule following an ECCE procedure. However, it some instances Ridley's early implants, dislocated inferiorly. This is believed to be due to the weight of the implant and the lack of equatorial capsular bag support due to the ECCE techniques of that time (Apple et al., 1984).

Following the difficulties incurred with posterior chamber implantation, many surgeons began to explore anterior chamber IOLs (AC IOL). Professor Peter Choyce was a strong advocate of the AC IOL and is credited with the first FDA approved anterior segment IOL based on adaptations to Strampelli's original designs (Choyce, 1979, Choyce, 1990, Pandey and Apple, 2005). From the 1950s to the 1970s, there were many incarnations of AC IOLs, unfortunately they were plagued with complications, such as corneal endothelial failure and chronic inflammation, thus gaining a poor reputation (Apple et al., 1984, Drews, 1982).

Following many advances to IOL design including advances in materials (allowing foldable IOLs) and introduction of haptics (flexible support arms to the IOL), IOLs finally became commonplace. Alongside the improvement to IOL design, there were significant improvements in surgical technique including the introduction of viscoelastic (to protect the cornea during surgery), the introduction of phacoemulsification and small self-sealing incisions (Allan, 2000).

1.7.2 Modern Intraocular Lenses

Modern IOLs consist of a central optic and haptics in the form of loops, arms or plate design. The optic provides the refractive power and the haptics anchor the IOL in place. There are now

many variations of commercially available IOLs. Early research in IOL design focussed on materials, surgical techniques and reducing posterior capsular opacification rates.

Posterior capsular opacification occurs when the remaining posterior capsule opacifies following cataract surgery. It is reported in 20-40% of patients, 2 – 5years after surgery (Awasthi et al., 2009). This is due to remnant lens epithelial cell proliferation and migration to the posterior capsule causing thickening and a loss of optical clarity. This can result in blurred or cloudy vision for the patient. It is rectified with a Nd:YAG laser capsulotomy (Awasthi et al., 2009).

Consequently, there are now a wide variety of foldable IOLs available in a multitude of materials. To this day, research in IOL design continues in order to optimise visual outcomes and reduce optical aberrations.

1.7.3 Intraocular lens materials

IOL materials must be biocompatible with the eye and optically clear. In addition, rigidity of a material is also important. The introduction of foldable IOL materials allows for smaller incision during surgery. Ridley's first IOL was made from PMMA (Ridley, 1952). PMMA lenses have excellent biocompatibility and high light transmissibility (Canovic, 2020). However, PMMA is a rigid non-foldable material, therefore are not able to pass through small incisions and thus have been superseded by modern foldable IOLs made from silicone or acrylic.

1.7.3.1 Silicone IOLs

The first foldable silicone IOL was implanted by Zhou in 1978 (Zhou, 1983). Silicone is a hydrophobic material with refractive index 1.41 to 1.46 (Canovic, 2020). There may be an

increased risk of post-operative infection with silicone IOLs due to bacterial adhesions (Baillif et al., 2009). In addition, silicone IOLs are contraindicated in individuals with high myopia due to the individual's risk of retinal detachment. When a silicone oil tamponade is used in retinal detachment surgery, silicone oil droplets adhere to the silicone IOL (Hu and Peng, 2018).

1.7.3.2 Hydrophobic acrylic IOLs

Hydrophobic acrylic IOLs are copolymers of acrylate and methacrylate derived from PMMA. They are foldable, thus can be manipulated and return to their original shape (Oshika and Shiokawa, 1996). Acrylic IOLs are typically of a higher RI than silicone IOLs, thus are thinner (Canovic, 2020). Hydrophobic IOLs have lower rates of posterior capsular opacification (PCO) (Leydolt et al., 2007).

1.7.3.3 Hydrophilic acrylic IOLs

Hydrophillic IOLs have excellent biocompatibility and are easily foldable (Canovic, 2020).

Higher PCO rates have been reported with hydrophilic IOLs (Findl et al., 2010, Kugelberg et al., 2006), however this may be due to edge design rather than material (Werner et al., 2009). There are also studies where no differences between the two materials for PCO rates have been noted (Iwase et al., 2011, Kang et al., 2009). However a recent meta-analysis concluded that hydrophobic IOLs have lower PCO rates (Zhao et al., 2017).

1.7.3.4 Hybrid IOLs

These IOLs are either surface coated or copolymer designs, for example some have a hydrophilic centre with a hydrophobic surface coating, thus giving the biomechanical

properties of a hydrophilic but maintaining the hydrophobic surface and less susceptibility to cell adhesions (Fujita et al., 2012). There are also Hybrid IOLs which are heparin coated thus reducing inflammatory cell adhesions (Taravati et al., 2012).

1.7.4 Intraocular Lens Designs

Typically, NHS cataract surgery involves implantation with the aim of achieving distance emmetropia. A single focus IOL (monofocal) can be used to correct spherical refractive errors and if there is significant corneal astigmatism pre-operatively then a toric IOL can be considered. Cataract surgery has developed to the extent that good unaided distance vision is now an expectation following cataract surgery (Calladine et al., 2012). This has likely been driven by the move to small incision phacoemulsification, and thus, greater predictability of refractive outcomes (Ang et al., 2012, Riaz et al., 2006). In addition, various IOLs are now manufactured in 0.25D steps. However, these patients still require reading spectacles after surgery (Javitt et al., 1997).

To date there are no IOLs that can replicate the full accommodative properties of the natural crystalline lens. In order to provide unaided distance and near vision, presbyopic solutions are required (Calladine et al., 2012).

In order to cater to spherical, astigmatic and presbyopic refractive errors, IOLs are commercially available in the following categories:

- Monofocal
- Toric
- Accommodating
- Multifocal

- Extended depth of focus

Accommodating, Multifocal (MIOL) and extended depth of focus (EDoF) IOLs are specifically designed to target presbyopia, however monofocal IOLs can also be used to provide a presbyopic solution.

There is some overlap in these categories, some EDoF IOLs use diffractive technology similar to MIOLs or target mild myopia in the non-dominant eye for a monovision effect (Cochener et al., 2014). Emerging technologies such as the Wichterle IOL- Continuous Focus have been reviewed in the literature as both an EDoF and an accommodating IOL (Kohnen and Suryakumar, 2020, Pepose et al., 2017).

In addition, to the above, there are various other IOLs in the developmental stage, with the aim of correcting presbyopia by altering refractive index (RI), either by two immiscible fluids of differing RI (Pepose et al., 2017) or by adjusting RI by means of an electrical stimulus (Li et al., 2006).

1.8 Monofocal Intraocular lenses

Monofocal IOLs provide a single focal length. They are typically used to correct distance vision (emmetropia), thus following surgery an individual would still require reading spectacles. However, they can be used to achieve a chosen refractive error. For example, an existing myope may prefer to remain myopic post-operatively, in order to avoid reading spectacles. Alternatively, should a patient only wish surgery in one eye, the surgeon may target a similar

refractive error to their pre-operative status to avoid anisometropia. Monofocal IOLs can be used to provide a presbyopic solution by creating monovision. Monovision utilises monofocal lenses, targeting emmetropia in the dominant eye and myopia in the non-dominant eye and this will be further discussed in section 1.10.

In addition to correcting refractive error, correction of higher order aberrations can also be considered. Cataract surgery and IOL implantation provide an opportunity to alter the aberrations affecting the eye (Denoyer et al., 2007, Sandoval et al., 2008). As such, there are many variants of monofocal IOLs available.

1.8.1 Higher Order Aberrations

We have already discussed lower order aberration, e.g. refractive errors such as myopia, hyperopia and astigmatism. However, the visual system is also affected by higher order aberrations (HOA), distortions that occur as light passes through the ocular media. These include spherical aberration and coma, which principally originate from the cornea and the crystalline lens (Artal and Guirao, 1998, Millodot and Sivak, 1979). Spherical aberration occurs when light passes through a spherical surface, the rays near the visual axis are refracted more or less than peripheral rays and as such there are slight variations in the final focal point, thus a less clear image is obtained. Coma or comatic aberration is a HOA, which results in a point focus having a trailing shape, like a comet. This occurs as off-axis rays pass through different parts of a spherical surface, thus they vary in magnification resulting in a comet shaped image. HOAs have a detrimental effect on visual acuity. The cornea induces positive spherical aberration in a youthful eye whilst the crystalline lens produces negative spherical aberrations. The aberrations of the crystalline lens approximately negate the corneal aberrations (Atchison et al., 2016). Research has shown that corneal aberrations remain relatively stable with age

(Guirao et al., 2000, Oshika et al., 1999, Wang et al., 2003). However, the total spherical aberration of an eye's optical system increases with age as the balance between the cornea and the lens is lost due cataractous changes creating increased positive spherical aberration (Glasser and Campbell, 1999, Rocha et al., 2007). Cataract formation has been found to affect higher order aberrations; nuclear sclerotic cataracts increase spherical aberration, yet cortical cataracts increase coma (Rocha et al., 2007).

Monofocal, spherical IOLs have positive spherical aberrations. The implantation of such IOLs increase the positive spherical aberration already induced by the cornea. As such, aspheric IOLs provide the means to minimise the effect of spherical aberration post implantation. There are two main designs of aspheric IOLs as discussed below.

1.8.2 Aberration control aspheric intraocular lenses

Aspheric optics on the anterior surface of the IOL can induce negative spherical aberrations, to compensate for the positive spherical aberration of the cornea (Cadarso et al., 2008, Rekas et al., 2009). Depending on their design, these IOLs induce a fixed magnitude of negative spherical aberration and therefore fail to account for variability in corneal spherical aberration between individuals. Spherical and coma aberrations in pseudophakic eyes implanted with aberration control aspheric IOLs have been found to be similar to the aberrations in phakic eyes of young individuals (Rekas et al., 2009). Other authors have also reported spherical aberration close to zero after implantation of these IOLs (Kretz et al., 2015c, Ohtani et al., 2009). Studies have shown that IOLs using aspheric technology provide good visual acuity and contrast sensitivity after cataract surgery (Ohtani et al., 2009, Rekas et al., 2009, Salvatore et al., 2011). The benefits of aspheric lenses can be limited by factors such as tilt and decentration, which induce coma (Altmann et al., 2005, Coppens et al., 2006, Wang and Koch, 2005). Using model eyes to

measure the effects of misaligned IOLs, Fujikado reported that whilst spherical aberration was similar in both spherical and aspheric lenses when tilted or decentered, vertical coma increased (Fujikado and Saika, 2014). When vertical coma was compared in misaligned spherical and aspheric lenses, it was found to be significantly higher in aspheric lenses, and aberrations were proportional to the spherical aberration corrective power of the lens (Fujikado and Saika, 2014). Subsequently, aspheric lenses show no true advantage over spherical counterparts in some instances (Schuster et al., 2013, Kasper et al., 2006).

1.8.3 Aberration neutral aspheric intraocular lenses

Aberration neutral aspheric lenses are designed to neither compensate for the positive spherical aberration of the cornea nor induce further aberrations to the optical system. As such these lenses are aberration neutral and therefore are minimally affected when an IOL is not positioned optimally in the capsular bag, whether it be tilted or decentered (Eppig et al., 2009). When compared to spherical monofocal IOLs these lens have been shown to improve visual outcomes (Caporossi et al., 2007).

1.9 Toric Intraocular lenses

Approximately 20-30% of patients undergoing cataract surgery have corneal astigmatism greater than 1.25 dioptres (D) (Day et al., 2019, Ferrer-Blasco et al., 2009, Hoffmann and Hutz, 2010) and approximately 40% have corneal astigmatism greater than 1.00D (Curragh and Hassett, 2017, Michelitsch et al., 2017). Uncorrected astigmatism is known to have an adverse

effect on distance visual acuity (Pesala et al., 2014, Wolffsohn et al., 2011). Thus, failing to correct this astigmatism at the time of surgery may lead to greater spectacle dependence after IOL implantation. Thus, we must also consider astigmatic solutions.

There are several methods available to provide astigmatic correction at the time of cataract surgery; peripheral corneal relaxing incisions (PCRIs) or limbal relaxing incisions (LRIs) as they are often referred to, and arcuate keratectomy/keratotomy (AK). All of these methods, involving making incisions in the corneal with the aim of flattening the cornea, a similar effect as seen in SIA, yet to a greater extent. The length of the incisions determines the extent of corneal flattening achieved and is decided by a nomogram (Hirnschall et al., 2014). These can be done manually or with a femtosecond laser. Both methods are dependent on the healing response of the cornea, and thus can be unpredictable (Kaufmann et al., 2005). Although greater refractive accuracy has been found with femtosecond laser incisions (Roberts et al., 2018). However, the corneal healing response does not influence the success of a toric IOL (TIOL).

TIOLs are IOLs with a toric correction incorporated into the optic. Efficacy of TIOLs relies on accuracy of both the pre-operative measurements of corneal curvature and calculation of TIOL power and orientation as discussed in section 1.6.7. The TIOL is implanted in the capsular bag and rotated to align with the steep corneal axis (Visser et al., 2013). However, the correction of astigmatism with a TIOL depends on precise alignment of the IOL with the principal astigmatic meridians. Rotation of the IOL reduces the effect of the IOL and less astigmatism is corrected. Small misalignments cause a relatively large effect on the level of correction as the relationship between alignment and residual astigmatism is sinusoidal rather than linear (Ma and Tseng, 2008). If an TIOL is rotated by 30° from its optimal axis, the astigmatic effect of the IOL is eliminated entirely (Felipe et al., 2011).

The use of TIOLs has been found to be an effective method of correcting corneal astigmatism surgically (Ahmed et al., 2010, Holland et al., 2010, Lake et al., 2019, Visser et al., 2011b), thus it has grown in popularity over the years (Amesbury and Miller, 2009). A randomised control trial comparing bilateral implantation of TIOLs with a control group with bilateral aspheric IOLs reported that 70% of patients with TIOLs achieved spectacle independence for distance vision compared to 30% in the control group (Visser et al., 2014).

1.9.1 IOL rotation

IOL rotation refers to the clockwise or anticlockwise rotation of the TIOL away from the axis of implantation post-operatively. If an IOL is placed centrally in the capsular bag then rotation can occur due to torque acting on the lens. This torque can be the result of gravity or ocular movements. In order to resist the effects of torque, tension between the haptics and the capsular bag and friction are required (Patel et al., 1999). However, compression of the haptics can also result in rotation. Rotational stability is required to ensure the TIOL remains at its optimal orientation (Potvin et al., 2016, Ribeiro et al., 2019).

The literature reports the influences of many factors on TIOL rotation (Buckhurst et al., 2010, Kaur et al., 2017, Li et al., 2020). Studies report that most IOL rotation occurs in the early post-operative period (Miyake et al., 2014, Prinz et al., 2011, Shimizu et al., 1994). Initial friction between capsule and TIOL and anterior chamber stability can affect the TIOL position. The smaller the IOL in relation to the size of the capsular bag, the greater the risk of rotation, due to less contact between the IOL and the bag (Chang, 2003). However, a large TIOL can result in stretching of the capsular bag (Lim et al., 1998). Residual OVD, either in front or behind the lens, can also alter its position (Myers and Olson, 1999). Intraocular pressure can drop following surgery, destabilizing the anterior chamber and thus increasing the risk of TIOL

rotation (Pereira et al., 2010, Shingleton et al., 2007). Whilst capsular fibrosis and shrinkage can also influence TIOL position, these factors occur later in the post-surgical period (Jampaulo et al., 2008, Zhu et al., 2016). It has also been reported that initial axial positioning affects rotation, with rotation more likely in those implanted close to the vertical axis (Prinz et al., 2011, Ruhswurm et al., 2000). However, others have found no difference in rotation despite axial positioning (Shah et al., 2012).

TIOLs are available in many of the platforms discussed in the monofocal and multifocal IOLs sections and the salient points apply, however when considering the rotational stability of the TIOL, material, dimensions and haptic design are of particular importance (Kaur et al., 2017).

1.9.2 IOL material

The materials used in manufacturing IOLs have developed through the decades. Most IOLs are now made from acrylic materials, whereas first generation IOLs were made from PMMA and thereafter silicone. Strong adhesions between the IOL and the anterior and posterior capsular bag are thought to prevent IOL rotation. Extracellular proteins, in particular, fibronectin which is available in the aqueous humour following cataract surgery, are thought to be responsible for IOL-capsular bag adhesions (Linnola et al., 2003). *In vitro* studies have examined the adhesions formed, comparing different IOL materials; hydrophobic, acrylic IOL materials show greater adhesive properties than hydrophillic, acrylic IOLs (Linnola et al., 2000, Linnola et al., 2003, Lombardo et al., 2009). Both acrylic lenses demonstrate greater adhesive properties than PMMA or silicone IOLs (Oshika et al., 1998). Hayashi (Hayashi et al., 2002) reported anterior capsular apposition at 6 days post implantation and posterior capsular apposition at 11 days post implantation in acrylic IOLs, thus expected that IOL rotation should be stabilised within 2 weeks of surgery, however in the first days stability relies on the haptics.

1.9.3 Haptic Design

TIOLs are available in lengths of 11 -13mm. Rotational stability has been shown to be greater amongst lenses with a longer overall length (Chang, 2003). Furthermore, TIOLs are available in a variety of haptic designs (Figure 1.10). The haptics make contact with the capsular bag and hold the lens in position, hence are vital in rotational stability.

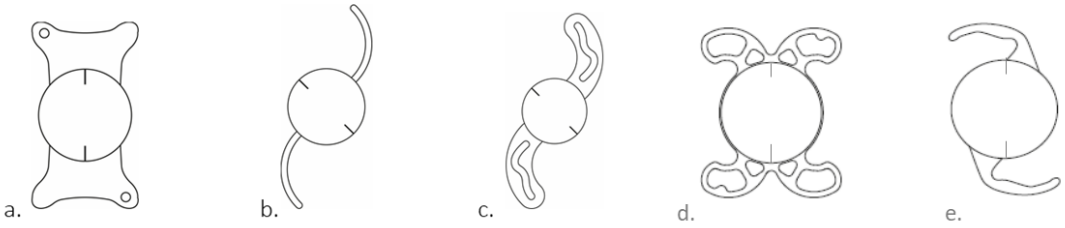


Figure 1.10: Haptic designs in toric IOLs

a. Plate haptic
b. Open C loop haptic
c. Closed loop haptic
d. Quadra loop haptic
e. Open Z loop haptic

1.9.3.1 Plate haptic Toric IOLs

Plate haptic IOLs (Figure 1.10a) demonstrate excellent long-term stability as they are less susceptible to compression forces in capsular contraction (Patel et al., 1999). Plate haptics have positioning holes which allow for easier manoeuvring during implantation. These holes also allow lens epithelial cells to migrate and can anchor the lens in place (Mamalis et al., 1996).

1.9.3.2 Open C Loop haptics

Open C loop haptics (**Figure 1.10b**) exert a centripetal pressure on the capsule bag and thus are held in place. This contact with the capsular bag is immediate on implantation, however, rotation can occur due to the compressive forces on the capsule bag and loop haptics typically experience clockwise rotation (Patel et al., 1999, Shimizu et al., 1994).

1.9.3.3 Closed loop haptics

Closed loop haptics (**Figure 1.10c**) have a second insertion on the IOL. They provide immediate contact with the capsule bag on implantation like an open loop haptic, but the effect of compressive forces is thought to be reduced as the outer haptic presses against the inner haptic during compression, locking the IOL in place. This is believed to improve rotational stability (Narendran et al., 2009).

1.9.3.4 Quadra loop haptics

Quadra loop haptics (**Figure 1.10d**) were designed to increase the area of friction between the haptics and the capsular bag, also the fenestrations allow contact between the anterior and posterior capsular, to improve rotational stability (Savini et al., 2019).

1.9.3.5 Open Z loop haptics

The Z design (**Figure 1.10e**) of the haptics exert expansile forces on the capsular bag, this is further aided by the corrugated nature of the haptic touching the capsular equator. This design was marketed to increase rotational stability however due to the design of the haptics, adjustment of rotation is more difficult and can only be done by compressing the haptics (De Silva et al., 2006).

1.9.3.6 Rotational stability due to haptic design

Randomised control trials have shown no agreement to date in the superiority of either open loop or plate-haptic design (Kessel et al., 2016). One study found that postoperative rotation stability was better in patients with open loop-haptic IOLs in the early post-operative period whereas, in the later post-operative period the plate haptics appeared more stable (Patel et al., 1999). In contrast, Chang proposed that open loop haptics provided better rotational stability overall (Chang, 2008). Yet, another study found no significant difference in stability between the designs (Prinz et al., 2011). Of note, both Chang and Patel compared larger total diameter acrylic open loop IOLs to small diameter silicone plate haptics, thus their findings may be influenced by other factors such as IOL total diameter or material (Chang, 2008, Patel et al., 1999). DeSilva (De Silva et al., 2006) reported rotationally stable outcomes with a Z loop design. A recent study evaluated a closed loop toric design and reported excellent rotational stability (Bhogal-Bhamra et al., 2019) and excellent rotational stability has also been reported with the quadraloop design (Savini et al., 2019).

1.9.4 Limitations of Toric IOLs

A systematic review (Kessel et al., 2016), observed promising figures for spectacle independence in TIOLs and concluded that the evidence base for the efficacy of TIOLs was positive, however further studies are required to concentrate on the potential complications when implanting TIOLs including rotational stability and toric calculations. In contrast, Hirnschall found that one-third of eyes following TIOL implantation failed to meet the target refraction (Hirnschall et al., 2014). Often the residual error is attributed to failure to consider posterior corneal astigmatism (Savini and Naeser, 2015) and this has prompted extensive work in recent years to improve nomograms and toric calculators (Abulafia et al., 2016, Eom et al.,

2015, Koch et al., 2013). Most lens manufacturers provide their own toric calculator, yet individual manufacturer calculators are not always investigated in the literature (Kern et al., 2018, Xue et al., 2018).

Many studies assess rotational stability at the slit lamp, however this must be viewed with caution as the results can be affected by cyclotorsion and head rotation, this may account for variations of approximately 2.5° between visits (Viestenz et al., 2006). High quality slit lamp photography is the preferred method of rotational assessment, where iris features and conjunctival vessels can be used to match images between visits, thus reducing inaccuracy due to head position and cyclorotation (Buckhurst et al., 2010, Wolffsohn and Buckhurst, 2010). Many of the published studies reporting rotational stability have not accounted for cyclorotation and thus further studies are required to truly evaluate post-operative rotation. In addition, it is known that rotation can occur due to capsular bag size and contraction, and capsular bag characteristics change with age and there are differences between individuals (Glasser, 2008), thus intra-patient comparative studies would limit the influence of capsular bag characteristics.

1.10 Monofocal Presbyopic Solutions

Monofocal IOLs can be used to provide a presbyopic solution. Monovision is induced by targeting emmetropia in one eye (usually the dominant eye) and myopia in the contralateral eye (Evans, 2007). When monovision in not targeted some pseudophakic individuals still achieve some near visual function in a process known as pseudo-accommodation.

1.10.1 Monovision

Monovision is a commonly used technique for providing a presbyopic solution. Optometrists provide monovision in contact lens practice (Efron et al., 2015) or it can be achieved by corneal refractive surgery (Xiao et al., 2011b). Pseudophakic monovision was first described by Boerner in 1984 (Boerner and Thrasher, 1984). The amount of myopia targeted in the non-dominant eye can be specific to the patient's lifestyle or if the patient has had a previous successful experience with monovision contact lenses, this can be replicated surgically. High satisfaction rates and spectacle independence have been shown with pseudophakic monovision (Finkelman et al., 2009, Ito et al., 2012).

1.10.2 Pseudo-accommodation with monofocal intraocular lenses

Pseudo-accommodation is the ability of a pseudophakic eye to provide correction for distance and correction for near beyond that expected due to the optics of the IOL (Patel et al., 2011). This is also known as apparent accommodation (Nakazawa and Ohtsuki, 1983, Nishi et al., 2006, Tsorbatzoglou et al., 2006). Multifocal IOLs provide distance and near vision by simultaneous perception (Section 1.11) but pseudo-accommodation can also occur with monofocal IOLs. Several factors have been suggested to be responsible for pseudo-accommodation: uncorrected astigmatism (Huber, 1981), increased depth of focus with small pupil size due to a pinhole effect (Nakazawa and Ohtsuki, 1983) and optical aberrations (Nishi et al., 2006, Oshika et al., 2002).

1.10.2.1 Uncorrected astigmatism

Mild myopic astigmatism if left uncorrected has been shown to aid the reading ability of pseudophakes (Patel et al., 2011). The increase in depth of focus in subjects with uncorrected against the rule myopic astigmatism has been shown in several studies (Datiles and Gancayco, 1990, Huber, 1981, Nanavaty et al., 2006, Sawusch and Guyton, 1991). Verzella (Verzella and Calossi, 1993) suggested that approximately 1.50D of uncorrected myopic astigmatism was optimal however, this may be detrimental to distance visual acuity (Patel et al., 2011).

Yet, Wolffsohn reported that uncorrected astigmatism was detrimental to both distance and near vision (Wolffsohn et al., 2011).

1.10.2.2 Pupil Size

Nakazawa investigated the relationship between pupil size and pseudo-accommodation and found them to be inversely proportional (Nakazawa and Ohtsuki, 1983). Smaller pupil sizes, like a pinhole, limit the light entering the eye, thus less peripheral rays and as such a smaller blur circle/circle of least confusion.

1.10.2.3 Higher Order Aberrations

Oshika (Oshika et al., 2002) assessed the relationship between pseudo-accommodation and corneal aberration and found that coma significantly correlated with apparent accommodation. This was further supported by Nishi (Nishi et al., 2006) who found a positive correlation between vertical coma and pseudo-accommodation.

Indeed aspheric IOLs have been shown to demonstrate lower levels of pseudo-accommodation than spherical monofocals due to the reduction in HOAs (Nishi et al., 2013).

Furthermore, low levels of chromatic aberration (when different wavelengths of light are focussed at different points on the focal plane) have been observed to reduce accommodation and depth of focus (Fincham, 1951). Blue light blocking IOLs show lower levels of chromatic aberration and as such pseudo-accommodation is found to be greatest in spherical clear IOLs when compared to both yellow aspheric and spherical IOLs (Marshall et al., 2005, Nishi et al., 2013).

Pseudo-accommodation should not be confused with pseudophakic accommodation, where there is forward movement of the IOL and capsular bag due to contraction of the ciliary muscle (Patel et al., 2011, Langenbucher et al., 2003). This process will be further discussed in section 1.11.

1.10.3 Limitations of Monofocal IOLs

Pseudo-accommodation with monofocal IOLs is multifactorial and therefore is not easily predictable thus is not viable as an independent presbyopic solution (Patel et al., 2011).

Extensive reports in the literature and a review in 2017 concluded that pseudophakic monovision was a useful and viable option for the correction of presbyopia delivering high levels of spectacle independence (Finkelman et al., 2009, Goldberg et al., 2018, Handa et al., 2004, Ito et al., 2009, Labiris et al., 2015, Labiris et al., 2017, Mahrous et al., 2018, Xiao et al., 2011a, Zhang et al., 2011). However, as with all methods of presbyopic correction, appropriate patient selection is vital. Consideration also needs to be given to the optimal level of monovision produced (Hayashi et al., 2011, Naeser et al., 2014), but this is likely to be patient specific rather than an arbitrary level that works for all. However, it has been shown that anisometropia (difference in refractive error between eyes) of >1.50D can cause disruption of

binocular vision and reduction in contrast sensitivity (Pardhan and Gilchrist, 1990). Yet, anisometropia of <1.50D is unlikely to affect binocular function (Evans, 2007). Evidence on the potential effect on stereopsis following monovision is also equivocal (Ito et al., 2009, Zhang et al., 2011). However, dysphotopsia (unwanted images following implantation, presenting as glare or halos typically) is reported to be less in monovision than in MIOLs (Labiris et al., 2015, Wilkins et al., 2013, Zhang et al., 2011).

1.11 Accommodating Intraocular lenses

Accommodating IOLs are intended to replicate the natural accommodative ability of the crystalline lens, by increasing the dioptric power of the eye with accommodative effort (Pepose et al., 2017). Various innovative technologies have been developed or are in development, to achieve an accommodative effect.

1.11.1 Position-Changing Accommodating IOLs

Theoretically, a fixed optic IOL could provide near vision if the IOL was displaced forward on attempted accommodation, however attempts have so far been limited in their success (Legeais et al., 1999). Model eye predictions suggest that a 1mm anterior displacement of an IOL could produce accommodation of 0.8D to 1.85D depending on the AL (Bennett, 1998) and corneal curvature of the eye (Nawa et al., 2003).

1.11.1.1 Single Optic Accommodating IOLs

Single optic accommodative IOLs have flexible haptics to allow the optic to shift anteriorly on ciliary muscle contraction, thus increasing the dioptric power of the eye (Menapace, 2007). However, the amplitude of accommodation provided is dependent upon the power of the IOL, with higher-powered lenses potentially enabling greater levels of accommodation (McLeod et al., 2003). Also, fibrosis of the capsular bag can restrict this forward movement, thus limiting the possible increase in dioptric power (Pepose et al., 2017). Various studies have used objective measures to assess accommodation or directly measured the anterior movement of the IOL, yet found accommodation to be insignificant (Cleary et al., 2010b, Dhital et al., 2013). However, when accommodation is measured subjectively, greater levels of accommodation have been noted (Cleary et al., 2010a). It has been reported that accommodative effect may in fact be due to HOAs, such as vertical coma as discussed in relation to pseudo-accommodation (1.10.2.3) rather than movement of the IOL in such lOLs, but not all studies have assessed HOA (Wolffsohn et al., 2010). Therefore subjective measures of accommodation will overestimate the accommodative effect as they measure both true accommodation and pseudo-accommodation (Cleary et al., 2010b).

1.11.1.2 Dual Optic Accommodative Intraocular lenses

Dual optic accommodative IOLs have two separate optics coupled by a hinged mechanism (McLeod et al., 2003, McLeod et al., 2007, Ossma et al., 2007). The anterior and posterior optics provide plus and minus power respectively. Capsular tension induced by contraction and relaxation of the ciliary muscle, alters the distance between the optics resulting in a change in the dioptric power of the eye. Dual optic accommodative IOLs have been shown to provide greater accommodative power than single optic accommodating IOLs (Alio et al., 2012b). The

dual optic design means that more accommodative power is created than in single optic designs with the same axial displacement (McLeod et al., 2007). Despite this, near vision was still limited (Tomas-Juan and Murueta-Goyena Larranaga, 2015).

1.11.2 Shape-changing Accommodating IOLs

Significant dioptric power changes can be achieved with alteration in curvature of the IOL, as naturally seen in the crystalline lens of young, phakic individuals. There are varying methods of achieving this; using a large diameter, haptic-free IOL to fill the capsular bag (Pallikaris et al., 2014) or by fluid flowing between hollow optics (Floyd et al., 2013). Another variation is a rigid PMMA base IOL with a central aperture through which silicone gel is extruded on accommodative effort (Alio et al., 2009, Ben-Nun and Alio, 2005, McCafferty and Schwiegerling, 2015). Theoretically, shape-changing IOLs should be the most efficient accommodating IOL as this is the closest mechanism to that of the phakic lens, however their ability to provide accommodation is yet to be demonstrated (Glasser, 2008).

1.11.3 Lens-Filling Accommodating IOLs

The concept of filling the capsular bag with a polymer and thus allowing shape changes was first proposed many years ago (Kessler, 1964, Parel et al., 1986). However, there are many challenges to this approach, including a high incidence of capsular opacification (Pepose et al., 2017). In addition, choosing a polymer with adequate viscoelastic properties and clarity, preventing leakage of the polymer and a suitable method of removal if required have presented challenges over the years (Pepose et al., 2017). Some of these challenges have been addressed by Nishi's work in principle (Nishi et al., 2008). In animal trials a 2.5D

accommodative effect was achieved in monkeys, but further work is needed before human trials can begin (Nishi et al., 2014). Increased accommodative effect was recorded in a study in human cadaver eyes, but *in vivo* studies are required to verify such findings (DeBoer et al., 2016).

1.11.4 Limitations of accommodative IOLs

The literature suggests that the anatomical structures involved in accommodation retain their function, thus it is feasible that true accommodation could be restored in pseudophakes (Koopmans et al., 2003, Glasser, 2006). However, despite the popularity of accommodative IOLs and the significant efforts in improving the designs of these implants, none of the commercially available accommodating IOLs have been able to truly replicate the accommodative ability of the crystalline lens (Glasser, 2008). The mean accommodative amplitude achieved is only approximately 1.50 dioptres (Kuchle et al., 2004) thus, near vision is still limited post-implantation (Tomas-Juan and Murueta-Goyena Larranaga, 2015). In addition, studies typically measure accommodation with subjective methods rather than objective, so true accommodative effect of significant magnitude is not yet proven (Cleary et al., 2010b, Glasser, 2008). A Cochrane review of the literature on accommodating lenses concluded that further research is required to understand accommodating IOLs and long-term studies are required to monitor the sustainability of the accommodative capability and near visual function of these implants (Ong et al., 2014). Subsequently, the volume of trials involving accommodating IOLs has waned suggesting that manufacturers are yet to overcome the issues inherent with these IOLs (Wolffsohn and Davies, 2019).

1.12 Multifocal Intraocular lenses

As a dynamic solution to restore accommodation has yet to be successful, the provision of distance and near visual function via static means is utilised. Multifocal spectacles (bifocals or varifocals) or contact lenses are routinely used in optometric practice as a presbyopic solution by providing two or more focal points. It is also possible to create multifocality with IOLs. Multifocal Intraocular lenses (MIOLs) separate light into different foci. The light is distributed between distance and near focal points whereby the vergence of the incident light dictates which focal point is conjugate to the retinal place. The number of foci or percentage of light focussed at each point is dependent on the design of the lens. This concept is known as simultaneous images (Davison and Simpson, 2006). The light energy distribution between focal points created by a MIOL influences the overall quality of vision at different viewing distances. MIOLs that split light equal create focal points of comparative image quality, yet distance dominant lenses (where a higher percentage of light is directed towards the distance focal point) have a relative compromise of near image quality. As such, the quality of the vision and the separation of the foci is also dependent upon the lens design. Multiple retinal images (two if the design is bifocal, three if the design is trifocal) are created (Breyer et al., 2017). Despite this only one image can be focussed on the retina at any given time; therefore unfocussed images are superimposed on focused images resulting in reduced contrast and the occurrence of photic phenomena (Calladine et al., 2012). The separation of these multiple focal points is determined by the addition power of the MIOL.

Multifocal IOLs are available as two principle designs:

- Refractive
- Diffractive

There are many important factors to consider regarding multifocal lenses and particular attention must be paid to the choice of multifocal IOLs for individual patients (Davidson et al., 2016).

1.12.1 Refractive Multifocal IOLs

Refractive IOLs use varying curvatures to create distinct areas of differing refractive power within the IOL. Refractive designs can be rotationally symmetric or asymmetric.

1.12.1.1 Concentric Designs (rotationally symmetrical)

Symmetrical designs use concentric circles (2 zone or multizone) to create the different powers. Early 2 zone designs (Figure 1.11), had a central circular area focussing for near and the periphery for the distance.

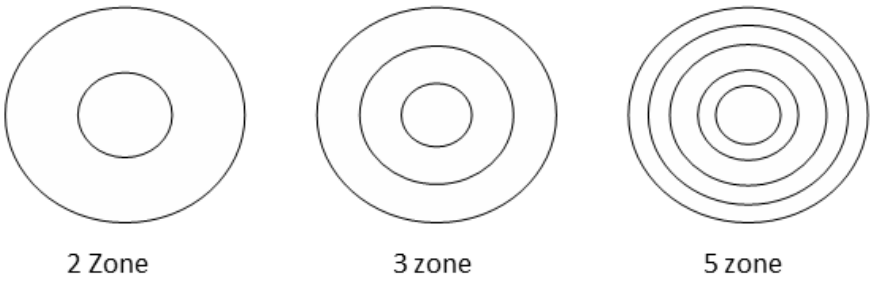


Figure 1.11: Multizone Refractive Design

Pupil size has been found to significantly affect the performance of these IOLs with reduced distance vision and contrast sensitivity being observed when viewed through a small pupil (<2.5mm) and reduced near vision and contrast sensitivity with large pupils (>6mm) (Atebara

and Miller, 1990). Although, using a central distance segment has been found to aid in achieving good distance visual acuity and contrast sensitivity even in small pupils (Kawamorita et al., 2009). In addition to pupil size, the centration of the IOL and location of the visual axis respective to the pupillary axis (angle kappa) are important factors (Hashemi et al., 2010). A large angle kappa may result in the visual axis only passing through the edge of the central zone (Prakash et al., 2011b). A decentered IOL may result in a similar scenario. The proportion of the near segment within the pupil margin can be reduced by decentration of the IOL (Percival, 1992).

Multizone designs use 3 or more concentric refractive areas (**Figure 1.11**). Three zone designs have been in commercial use but the evaluation of 5 zone designs is more extensive (Cillino et al., 2008, Fujimoto et al., 2010, Montes-Mico et al., 2004, Pieh et al., 2001). Such IOLs are characterised by five refractive zones on the anterior surface with a central distance circular zone surrounded by four annular zones of increasing diameter. These zones alternate between distance and near. Five zone IOLs are still pupil dependent as each refractive zone is relatively large, however pupil dependency is less than in two or three zone models and as such they are less sensitive to decentration (Fujimoto et al., 2010).

1.12.1.2 Segmental Designs (rotationally asymmetric)

Segmental or sectorial refractive multifocal IOLs have a segment of the lens with a near addition power. This near segment is embedded typically in the posterior lens surface (**Figure 1.12**).

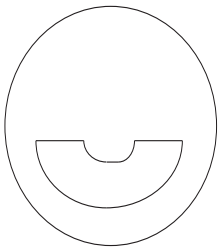


Figure 1.12: Segmental Optic

Initially, manufacturers recommended that these IOLs be implanted with the near segment inferiorly, but studies have shown that the IOL is also well tolerated when placed superiorly or supero-temporally (McNeely et al., 2016b, de Wit et al., 2015). Good levels of near and intermediate vision have been recorded with segmental refractive multifocal IOLs (Alio et al., 2012a, McAlinden and Moore, 2011, McNeely et al., 2016a).

1.12.2 Diffractive Multifocal IOLs

Diffraction patterns occur when light encounters a boundary/edge or aperture in the medium through which it passes. Diffractive multifocal IOLs are based upon the principle of diffraction to create multiple focal points (Jay et al., 1991). The anterior or posterior surface of the IOL, has a diffractive pattern. Concentric rings create boundaries (steps) across the surface and as the light encounters these boundaries, there is a phase delay and a change of direction. An interference pattern is achieved creating multiple orders of light.

With regard to multifocal IOLs, the spacing (wavelength) between each step determines the focal point of the 1st order. The smaller the spacing, the greater the vergence and hence the higher the addition power of the IOL (Figure 1.13).

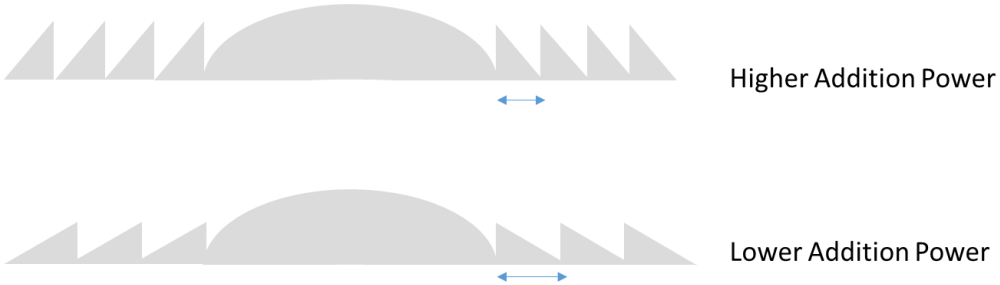


Figure 1.13: Diffractive Patterns

The height of the steps also determines the percentage of incident light distributed to each diffractive order. If the step height changes by the same amount across the whole optic then distribution of light to each order also remains constant. Not all light is directed to the desired focal points with a diffractive pattern, as light is lost to the higher orders (Hutz et al., 2006). If the light is split equally between distance and near, only 41% transmission is achieved at each focal point, 18% is lost to higher orders (Hutz et al., 2006).

Apodisation is the process in which step sizes gradually reduce towards the periphery of the IOL optic (Figure 1.14). Thus, as the pupil size increases and more of the optic is revealed, the reduced step size ensures that a higher percentage of the incident light is directed to the 0^{th} order (distance foci).

Figure 1.14: Apodised Diffractive Profile

1.12.2.1 Fully Diffractive IOLs

Fully diffractive IOLs have a diffractive pattern across the entire optic of the lens (Figure 1.15). These lenses can be pupil independent if they are non-apodised as the light distribution remains constant irrespective of pupil size. In contrast, apodised lenses are pupil dependent.

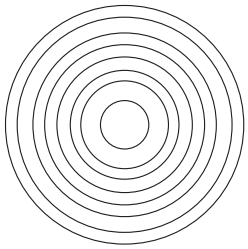


Figure 1.15: Diffractive Optic

1.12.2.2 Partially Diffractive IOLs

Partially diffractive IOLs (Figure 1.16) have a central diffractive pattern but the peripheral optic is refractive in design and these lenses are pupil dependent. As the pupil size increases the distance dominant refractive peripheral optic is exposed. If the central diffractive area of the optic is non-apodised the lens can be described as pupil independent within a range of pupil sizes. For example; the Carl Zeiss Meditec AT LISA 839MP is described as pupil independent up to 4.34mm (www.zeiss.com).

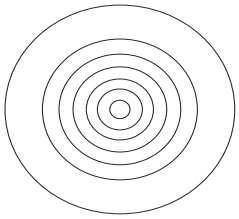


Figure 1.16: Partially Diffractive Optic

Diffractive lenses are available in spherical and aspheric designs, with the same advantages and disadvantages as their monofocal counterparts. Studies have found either equal visual performance when comparing spheric and aspheric multifocal IOLs (de Vries et al., 2010) or superior visual performance with an aspheric multifocal IOL (Alfonso et al., 2009b).

Pupil dependent lenses are not recommended in patients who have pupillary irregularities or abnormally large or small pupil diameters.

1.12.3 Trifocal Diffractive IOLs

Bifocal IOLs utilise two focal points and are commonly used to provide both distance and near vision (Alfonso et al., 2009a, Auffarth et al., 1993, Blaylock et al., 2006, Petermeier et al., 2011). However, these IOLs have a reduced intermediate range which can affect the patient's satisfaction (Petermeier et al., 2009a). Consequently, this has since led to the development of trifocal IOLs with improved visual function in the intermediate range. The diffraction patterns described afore are still applied in trifocal designs, but in order to achieve trifocality, two harmonic bifocal diffractive patterns are combined, where the near addition is equal to double the intermediate addition (Figure 1.17). The first pattern is distance-intermediate and the second distance-near with alternating steps between the two profiles.

Figure 1.17: Trifocal Diffractive Pattern

In a bifocal design, the 0^{th} order equates to distance vision, the 1^{st} order to near and 2^{nd} order and beyond is "lost" light. In the trifocal design, the 0^{th} order focuses for distance vision (the combination of diffractive patterns 1 and 2), the 1^{st} order is intermediate focus (pattern 1) and near focus is achieved by the 1^{st} order diffraction of diffractive pattern 2. Thus, light that would otherwise be lost is utilised in augmenting the near focus.

For example in a bifocal with +3.50D Addition power, order 0 is focussed for distance, 1^{st} order at +3.50D and 2^{nd} order would have vergence of +7.00D (double the first order). This 2^{nd} order generates an additional focal point, however it has a focal length that is too close to provide useful vision.

However, if this principle is applied to trifocal, if the +3.50 and +1.75 Addition power diffractive pattern are combined. Pattern 1 has 0 order, distance focus and 1^{st} order +3.50D, 2^{nd} order is list, however pattern 2 has 0 order for distance, 1^{st} order +1.75D, 2^{nd} order will occur at +3.50D, thus augmenting pattern 1.

Thus, trifocals are expected to provide improved intermediate vision compared to bifocals and this has been confirmed by a meta-analysis comparing visual performance of bifocal and trifocal IOLs. The study found that trifocal IOLs were able to provide significantly improved intermediate visual acuity without significantly compromising either distance or near visual acuity (Xu et al., 2017). In addition, studies have also shown contrast sensitivity results with trifocals to be equivalent to bifocals despite the addition of a third focal point (Alio et al., 2018a, Cochener, 2016, Mojzis et al., 2014, Plaza-Puche et al., 2016).

1.12.4 Quadrafocal IOLs

In 2015, Kohnen implanted the first reported quadrafocal IOL, the Acrysof IQ Panoptix (Alcon Laboratories,Inc) (Kohnen, 2015). This lens is also referred to as a panfocal IOL (Bohm et al., 2018). It has visual functionality similar to that of a trifocal with focal points achieved at distance, 60cm and 42cm (Lee et al., 2016). However, a 4^{th} focal point is also created at 1.2m, which is redistributed to the distance focal point and thus is used to improve light efficiency for distance focus (Kohnen, 2015). Comparative studies show similar performance with existing trifocal IOLs (Bohm et al., 2018, Lawless et al., 2017, Martinez de Carneros-Llorente et al., 2019).

1.12.5 Limitations of Multifocal Intraocular Lens

As previously discussed, intermediate vision is limited in bifocal IOLs. Mix and match with different addition powers has been useful in bifocal implantation to increase spectacle independence (Gundersen and Potvin, 2016, Hayashi et al., 2015). Bilateral implantation of trifocal IOLs has been shown to have better intermediate visual acuity than mix and match bifocals (Bilbao-Calabuig et al., 2016, Gundersen and Potvin, 2016). This improvement in intermediate vision and non-inferiority in other visual metrics has been widely published for trifocal IOLs (Alio et al., 2018a, Cochener, 2016, Plaza-Puche et al., 2016, Xu et al., 2017).

Positive Dysphotopsia is a visual disturbance resulting from non-conformities in the IOL resulting in glare or halos around light sources. It is universally accepted that MIOLs will result in dysphotopsia (Woodward et al., 2009), however, the extent of these disturbances and clinical significance is still a subject of debate principally due to the varying methodologies used to quantify such phenomena (Buckhurst et al., 2017). It is also questionable whether specific designs are less likely to cause symptomatic dysphotopsia. Refractive MIOLs were reported to

minimise glare and halos compared to diffractive MIOLs (Alio et al., 2012a), yet other studies disagree (Cillino et al., 2008, Shao and He, 2014, van der Linden et al., 2012). MIOLs are also associated with reduced contrast sensitivity (Cillino et al., 2008) especially in mesopic (dim) lighting conditions (Hayashi et al., 2009). However, this appears to be consistent across the designs (Mesci et al., 2010), and still falls within the age-related ranges expected in phakic individuals (Alfonso et al., 2010, Montes-Mico et al., 2004).

Negative dysphotopsia is also a well-documented phenomena, where a temporal crescent-shaped shadow is apparent, however this is reported in many pseudophakic individuals and is not exclusive to multifocals (Davison, 2000)

Angle Kappa is the angle between the visual axis and pupillary axis (Hashemi et al., 2010). Clinically, it can be identified as the displacement of the corneal light reflex from the pupil centre (Park et al., 2012). A large angle kappa can contribute to functional decentration of a MIOL and lead to patient dissatisfaction as the visual axis will no longer pass through the centre of the lens, thus less than optimal visual performance of the MIOL (Prakash et al., 2011a, Prakash et al., 2011b, Rosales et al., 2010). Caution should be exercised when implanting IOLs in patients with small pupil diameters with a pre-operative photopic pupil of >3mm being desirable for MIOLs (Fujimoto et al., 2010, Kawamorita and Uozato, 2005, Moore et al., 2017). Reduction in contrast sensitivity has been reported in small pupils with diffractive MIOLs (Ouchi and Shiba, 2018).

Despite all of these factors the main reason for dissatisfaction in MIOLs is attributed to uncorrected refractive error (Gibbons et al., 2016, de Vries et al., 2011). It is clear that there are many clinical outcomes that should be assessed with MIOLs in order to fully understand the function of differing lenses.

1.13 Extended Depth of Focus Intraocular lenses

Extended depth of focus (EDoF) IOLs were designed as an alternative to bifocal and trifocal MIOLs, primarily to improve the range of vision especially in the intermediate zone (Bellucci and Curatolo, 2017). They were also initially introduced to the market claiming to have less severe visual disturbances (dysphotopsia) than diffractive MIOLs (Cochener and Concerto Study, 2016). In order to classify an IOL as EDoF, it must meet the criteria outlined by the American Academy of Ophthalmology (AAO); and must have a depth of focus (DoF) ≥ 0.50D greater than a monofocal control at 0.20LogMAR (MacRae et al., 2017).

There are 4 main types of EDoF IOLs currently available;

1. Small Aperture Design
2. Bioanalogic Design
3. Diffractive Optics
4. Non-diffractive Optics

1.13.1 Small Aperture Design

The IOL has a small aperture centrally, with an opaque surround (**Figure 1.18**) which is implanted in one eye only, to achieve a pinhole effect. However, caution must be exercised in patients with large pupils (Dick et al., 2018, Grabner et al., 2015).

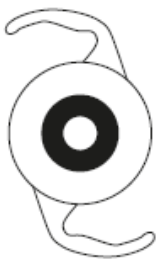


Figure 1.18 Small Aperture EDoF IOL

1.13.2 Bioanalogic Design

Using a bioanalogic hydrogel material, with a large diameter and no haptics, these IOLs aim to emulate the crystalline lens (Studeny et al., 2016). It has a refractive power that decreases from the centre to the periphery, however there is limited literature reporting on the clinical outcomes of this type of IOL (Kohnen and Suryakumar, 2020, Siatiri et al., 2017, Studeny et al., 2016).

1.13.3 Diffractive Optics

These IOLs use a central diffractive pattern (Cochener and Concerto Study, 2016) or a continuous diffractive pattern (Kretz et al., 2018). One of the commercially available EDoF lenses uses a combination of diffractive technology and the correction of chromatic aberration to maintain good distance VA (Weeber et al., 2015). The aspheric nature of the IOL creates negative spherical aberration to neutralise the positive spherical aberration of the cornea and correct the ocular chromatic aberration. The diffractive lens provides negative dispersion enabling the correction of chromatic aberration (Stone and George, 1988).

1.13.4 Non-diffractive Optics

These IOLs rely on manipulations of spherical aberration to achieve extended depth of focus. The central zone induces positive spherical aberration, whilst the mid zone provides negative spherical aberration and the periphery of the IOL is monofocal (**Figure 1.19**) (Bellucci and Curatolo, 2017).

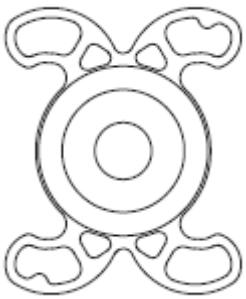


Figure 1.19: Non-diffractive EDoF IOL

1.13.5 Limitations of Extended depth of focus IOLs

EDoF IOLs have been shown to provide improved intermediate and near visual acuity when compared to monofocal IOLs (Bellucci and Curatolo, 2017, Kohnen and Suryakumar, 2020) however, the near vision is inferior to that achieved in a MIOL (Webers et al., 2020). Contrast sensitivity has been reduced in some studies (Dick et al., 2017, Gundersen and Potvin, 2020) and there are conflicting reports regarding the distance vision outcomes (Cochener and Concerto Study, 2016, Savini et al., 2018b). Dysphotopsia is still reported in subjects (Escandon-Garcia et al., 2018, Liu et al., 2019). EDoF IOLs have been marketed as likely to produce less dysphotopsia, due to a less diffractive rings on the optic (Cochener and Concerto Study, 2016) and only minimal dysphotopsia has been reported in non-diffractive EDoF IOLs (Giers et al., 2019). However, literature has shown that increasing positive or negative spherical aberration will increase the light distortion in a pseudophakic eye and as EDoF IOLs use negative spherical aberration, this may explain why dysphotopsia still occurs (Macedo-de-Araujo et al., 2016). Hence, EDoF IOLs may not be the optimum solution for presbyopic correction (Kasper et al., 2006).

1.14 Analysis of Multifocal Intraocular Lenses

The basic aim of cataract surgery is to restore visual function. As such distance vision, residual refractive error and distance visual acuity are routine clinical outcome measures post-operatively and excellent outcomes with monofocal IOLs have long been established (Desai, 1993, Desai et al., 1996). Advances in surgical techniques, IOL calculations and IOL designs allow the opportunity to not only restore function but also potentially correct pre-operative refractive errors, including astigmatism and presbyopia, as such a wider range of clinical outcome measures should be employed. The literature review conducted for this thesis has outlined the array of IOL designs commonly available and describes the potential benefits of each. Yet there remain limitations both in our understanding of the benefits and limitations of different IOLs and in the standardisation of assessment techniques. The benefits and limitations of different IOLs must be fully explored in order to have a clear understanding of differing IOL functionality and thus, offer prospective patients a guided and comprehensive outline to ensure their post-operative expectations are realistic. The next section will review previous systematic reviews to outline current knowledge into the effectiveness of MIOLs (section 1.14.1), differences in outcome measurement (1.14.2) and study follow up (1.14.3).

1.14.1 Reviews of the effectiveness of IOLs

Systematic reviews are a type of literature review that identify and appraise published material that meet a pre-defined specified eligibility criteria and address a specific research question. A Cochrane Review is a systematic review that has been compiled with the supervision of the Cochrane Review group and is published by the Cochrane systematic review database.

1.14.1.1 Systematic reviews of MIOL studies

Cochrane reviews in 2006 and 2012 reviewed randomised control trials (RCT) comparing MIOLs to monofocal IOLs, both concluded that near vision and spectacle independence in MIOLs was improved but highlighted inconsistency with methods, particularly when assessing near vision (Calladine et al., 2012, Leyland and Pringle, 2006). They reviewed only RCTs, as MIOL studies without a monofocal control were regarded as relatively uninformative.

Leyland stated that current methods of near vision reporting made comparison between studies difficult and that future studies should strive for clarity in reporting (Leyland and Pringle, 2006). Calladine concluded that a core set of outcomes measures were required when evaluating MIOLs (Calladine et al., 2012).

A further Cochrane review, with the same aims, was carried out in 2016 (de Silva et al., 2016), their database search identified over 800 further MIOL studies (2012 to 2016), yet only five new RCTs were identified. Like previous reviews, DeSilva called for further RCTs examining the efficacy of MIOLs over monofocal IOLs and standardisation of outcomes measures (de Silva et al., 2016).

The 20 RCT studies that were included in the 2016 Cochrane Review are detailed in **Table 1.1 (a-d),** (Cillino et al., 2008, el-Maghraby et al., 1992, Haaskjold et al., 1998, Harman et al., 2008, Javitt and Steinert, 2000, Ji et al., 2013, Jusufovic, 2011, Kamlesh et al., 2001, Labiris et al., 2015, Leyland et al., 2002, Martinez Palmer et al., 2008, Nijkamp et al., 2004, Peng et al., 2012, Percival and Setty, 1993, Rasp et al., 2012, Rossetti et al., 1994, Sen et al., 2004, Steinert et al., 1992, Wilkins et al., 2013, Zhao et al., 2010). There is significant overlap in the lenses used in these studies and as such only 10 different MIOLs are included, thus there are many available MIOLs which have not been compared to a monofocal.

Table 1.1: Summary of studies included in 2016 Cochrane Review

Author	Lenses used	Lens Description	No of patients	Eye	Masked	Visits	Tests	Comments
Cillino 2008	AMO Array SA-40N	Concentric Refractive +3.50 Add	16	Bilateral	Double blind	1/7 1/52 1/12 3/12 6/12 12/12	UDVA and BCVA Snellen DCNVA BCNVA UCIVA DCIVA Sloan letter near charts Defocus +2 to -5 (1D Steps) CS (VCTS-6500) QoV questionaire	
	AMO ReZoom	Concentric Refractive +3.50 Add	15					
	AMO Tecnis ZM900	Fully Diffractive +4.00D Add	16					
	AMO AR40	Monofocal	15					
el Maghraby 1992	3M/Vision Care 815LE	Partially diffractive +3.50 Add	39	Unilateral	Not specified	2-4/52 2-4/12	Jaeger Near vision UDVA and CDVA Snellen	
	3M 15LE	Monofocal	38					
Haaskjold 1998a	Pharmacia 808X	Diffractive Bifocal +3.50 Add	115	Unilateral	Not specified	5/12	CS VCTS 6500 Chart (3 light levels)	multicentre
	Pharmacia 808D	monofocal	106					
Harman 2008	AMO Array SA-40N	Concentric Refractive +3.50 Add	30	Bilateral	Double blind	3/12 18/12	UDVA and CDVA ETDRS RAF Rule Defocus (+3 to -5) (1D Steps) Binocular UNVA and DCNVA with Bailey Lovie MN Read (reading speed) CS Pelli Robson Glare (BAT) QoV	Multifocal and monofocal are same platform
	1CU	Accommodating	30					
	AMO Clariflex	Monofocal	30					
Javitt 2000	AMO Array SA-40N	Concentric Refractive +3.50 Add	64	Bilateral	Double blind	3/12	TyPE questionnaire UDVA, CDVA UNVA, DCNVA Snellen and regan converted to LogMAR	Same platform lenses Multicentre
	AMO Phacoflex II	Monofocal	60	Bilateral				

UDVA unaided distance visual acuity, **CDVA** corrected distance visual acuity, **UIVA** unaided intermediate visual acuity, **UNVA** unaided near visual acuity, **CIVA** corrected intermediate visual acuity, **CNVA** corrected near visual acuity, **DCIVA** distance corrected intermediate visual acuity, **DCNVA** distance corrected near visual acuity, **CS** contrast sensitivity

Table 1.1b: Summary of studies included in 2016 Cochrane Review

Author	Lenses used	Lens Description	No of patients	Eye	Masked	Visits	Tests	Comments
Ji 2013	Alcon Acrysof ReSTOR	Partially Diffractive +3.00D Add	24 (30 eyes)	Mixed	Not specified	1/52 1/12 3/12	ETDRS 4m CDVA and UNVA CS (CGT-1000) Jaegar Near Vision Aberrometry	Monocular implantation mostly
	Alcon Acrysof Natural	Monofocal	27 (34 eyes)					
Jusufovic 2011	AMO ReZoom	Concentric Refractive +3.50 Add	50	Unilateral	Double blind	6/52	UDVA (Snellen converted to decimal) Jaegar Near Stereopsis	Some patients pre-presbyopic (youngest age 20) No comment on 2nd eye VA
	Alcon AcrySof MA60BM	Monofocal	50					
Kamlesh 2001	Domilens Progress 3	Partially diffractive +5.00D Add	20		Not specified	1/52 3/52 6/52 3/12	Defocus -5 to 5 (0.5D Steps) QoV questionnaire Snellen Acuity Pelli Robson CS	Unclear implantation and/or VA monocular or binocular
	Domilens Flex 65	Monofocal	20					
Labiris 2015	Hoya Isert PY60MV	3 zone concentric Refractive +3.00D Add	37	Bilateral	Not specified	6/12	UDVA UNVA ETDRS charts Pelli Robson CS Stereopsis QoV questionaire	Monofocal group targeted monovision of -1.25 non-dom
	Alcon SN60WF	Monofocal	38					
Leyland 2002	AMO Array SA-40N	Concentric Refractive +3.50 Add	29	Bilateral	Double blind	12/52 50/52 65/52	ETDRS UDVA and CDVA UNVA and DCNVA Bailey-Lovie Near Chart Defocus +3 to -5 (1.0 Dsteps) Pelli Robson CS Glare disability (BAT) TyPE questionarie	
	Storz TRUEVISTA	Concentric Refractive +4.00 Add	15					

UDVA unaided distance visual acuity, **CDVA** corrected distance visual acuity, **UIVA** unaided intermediate visual acuity, **UNVA** unaided near visual acuity, **CIVA** corrected intermediate visual acuity, **CNVA** corrected near visual acuity, **DCIVA** distance corrected intermediate visual acuity, **DCNVA** distance corrected near visual acuity, **CS** contrast sensitivity

Table 1.1c: Summary of studies included in 2016

Author	Lenses used	Lens Description	No of patients	Eye	Masked	Visits	Tests	Comments
Martinez-Palmer 2008	AMO ReZoom	Concentric Refractive +3.50 Add	32	Bilateral	Double blind	1/7 1/12 3/12	UDVA and CDVA (Snellen) Monoular and binocular UNVA and DCNVA CS (FACT) QoV final visit	
	Acri.Tec Twin Set	Partially Diffactive +4.00 Add	32					
	AMO Tecnis ZM900	Fully Diffractive +4.00D Add	26					
	AMO Tecnis Z9000	Monofocal	24					
Nijkamp 2004	AMO Array SA-40N	Concentric Refractive +3.50 Add	78	Bilateral	Yes (only at first visit)	3/12 after 1st eye and after 2nd eye	ETDRS UDVA, CDVA UNVA and CNVA Jaeger converted to logMar QoV questionaire	
	AMO phacoflex	monofocal	75					
Peng 2012	Alcon Acrysof Restor	Partially Diffractive +3.00D Add	51		Masked clinician	1/7 1/12 6/12	UDVA, CDVA UNVA, DCNVA UIVA, DCIVA all ETDRS charts Defocus (+2 to -5)(0.5) Cquant straylight MTF iTrace	Also measured tilt and decentration with pentacam
	Acrysof IQ		51					
Percival 1993	AMO Array	Concentric Refractive +3.50 Add	30		Not specified	4-6/12	Snellen Acuity CS with Regan Chart Px's were asked if they used glasses	Same platform lenses
	AMO PC25	Monofocal	25					
Rasp 2012	AMO Rezoom	Concentric Refractive +3.50 Add	143	Bilateral	Not specified	12/12	Bilateral UDVA, CDVA Reading speed Reading distance	
	AMO Tecnis ZMA00	Fully Diffractive +4.00 Add	26					

UDVA unaided distance visual acuity, **CDVA** corrected distance visual acuity, **UIVA** unaided intermediate visual acuity, **UNVA** unaided near visual acuity, **CIVA** corrected intermediate visual acuity, **CNVA** corrected near visual acuity, **DCIVA** distance corrected intermediate visual acuity, **DCNVA** distance corrected near visual acuity, **CS** contrast sensitivity

Table 1.1d: Summary of studies included in 2016 Cochrane

Author	Lenses used	Lens Description	No of patients	Eye	Masked	Visits	Tests	Comments
Rasp (cont) 2012	AT LISA 366D	Partially Diffractive + 3.75 Add	30					
	Acrysof Restor SN6AD3	Partially Diffactive +4.00 Add	28					
	Acri.Smart	Monofocal	29					
Rossetti 1994	3M/Vision Care 815LE	Partially diffractive +3.50 Add	38	Unilateral	Not specified	3/12 6/12 12/12	UDVA, CDVA ETDRS Jaegar Near Pelli Robson VF7 QoV	
	3M/Vision Care 15LE	Monofocal	42					
Sen 2004	AMO Array SA-40N	Concentric Refractive +3.50 Add	35 (53 eyes)	Mixed	Not specified	1/52 1/12	UDVA, CDVA Snellen UNVA Jaegar CS VCTS 6500 QoV	
	AMO SI-40NB	Monofocal	40 (67 eyes)					
Steinert 1992	AMO Array SA-40N	Concentric Refractive +3.50 Add	32	Unilateral	Double blind	3/12	Defocus (-6 to +6 vary increment) UDVA, UNVA and DCNVA with Regan charts, Jaegar/Rosenbaumcharts for near QoV Glare (BAT)	Same platform lenses
	AMO PC-25NB	Monofocal	30					
Wilkins 2013	AMO Tecnis ZM900	Fully Diffractive +4.00D Add	106	Bilateral	Not specified	4/12	UDVA, UIVA, UNVA	Monovision -1.25 Multicentre
	B&L Akreos	Monofocal	106					
Zhao 2010	Alcon Acrysof Restor	Partially Diffactive +4.00 Add	72	Unilateral	Double blind	1/52 1/12	QoV (VF7) CS VCTS 6500	
	Alcon SA60AT	Monofocal	89			6/12	Snellen and sloan charts	

UDVA unaided distance visual acuity, **CDVA** corrected distance visual acuity, **UIVA** unaided intermediate visual acuity, **UNVA** unaided near visual acuity, **CIVA** corrected intermediate visual acuity, **CNVA** corrected near visual acuity, **DCIVA** distance corrected intermediate visual acuity, **DCNVA** distance corrected near visual acuity, **CS** contrast sensitivity

This was also noted by a systematic review in 2011, where the majority of IOLs implanted in the included studies was the same diffractive bifocal (AcrySof ReStor)(Cochener et al., 2011). Wang's (Wang et al., 2017) systematic review in 2017, specifically assessing studies of premium IOLs (MIOLs, accommodating IOLs and toric IOLs) that reported on the following outcome measures; dysphotopsia, contrast sensitivity, spectacle independence, quality of life and IOL exchange.

In 2017, a further systematic review was conducted by Wang (Wang et al., 2017). He commented on the lack of recent RCTs comparing modern MIOLs to monofocals. The RCTs included in his review (those also in 2016 Cochrane review) mostly pertain to older models of MIOLs, with higher addition powers thus, he concluded their relevance in now somewhat limited. Khandelwal (Khandelwal et al., 2019) conducted a systematic review in 2019, it included the 20 studies from the 2016 Cochrane review and an additional 5 studies were also included. For some outcome measures they were able to divide the MIOLs into an older generation and newer generation groups and concluded that newer generation MIOLs have better near vision and less dysphotopsia than older generation lenses. Thus, RCT comparison of current MIOL designs to monofocal IOLs is required as the current evidence base has become outdated and may lead to false assumptions regarding the performance of current MIOLs.

1.14.1.2 Cochrane Review of Bifocal and Trifocal studies

A recent Cochrane Review (Zamora-de La Cruz et al., 2020) analysed RCTs comparing bifocal and trifocal IOLs. They identified 5 qualifying studies from their database search of >3000 studies (Cochener, 2016, Jonker et al., 2015, Kaymak et al., 2017, Mojzis et al., 2014, Mojzis et al., 2017). The 5 RCTs are detailed in Table 1.2. There was significant overlap, thus only 5

different MIOLs (3 bifocals and 2 trifocals) were assessed. The Cochrane Review concluded that there was inconclusive evidence relating to contrast sensitivity and quality of life, and recommended that future studies should evaluate contrast sensitivity, quality of life measures and halos/glare in addition to visual acuity.

Table 1.2: Summary of studies included in 2020 Cochrane Review

Author	Lenses used	Lens Description	No of patients	Eye	Masked	Visits	Tests	Comments
Mojzis **2014**	AT LISA 801	Diffractive Bifocal +3.75Add	15	Bilateral	Yes(subjects) No(clinician)	3/12	UDVA,CDVA (LogMAR) UIVA, CIVA,DCIVA (66 and 80cm) UNVA, CNVA,DCNVA (33 and 40cm) Defocus (+1.00 to-4.00) (0.50steps) Contrast Sensitivity (CSV-1000) Ocular Aberations (OPD-Scan III)	
	AT LISA 839MP	Diffractive Trifocal +3.33 Add	15					
Jonker **2015**	FineVision	Diffractive Trifocal +3.50Add	15	Bilateral	Yes	1/12 3/12 6/12	UDVA, UIVA(70cm), UNVA(40cm) Defocus (+2.00 to -5.00)(0.50steps) Contrast Sensitivity(CSV-1000) Reading Speed QoV Satisfaction and Spectacle independence	Photopic and mesopic
	AcrySof IQ Restor	Diffractive Bifocal +3.00Add	13					
Cochener **2016**	FineVision	Diffractive Trifocal +3.50Add	15	Bilateral	Not stated	6/12	UDVA, CDVA (LogMAR) UIVA, DCIVA (66cm) UNVA, DCNVA (33cm) Contrast sensitivity Defocus QoV	
	Tecnis ZMB00	Diffractive Bifocal	12					
Mojzis **2017**	AT LISA 801	Diffractive Bifocal +3.75Add	18	Bilateral	Yes(subjects) No(clinician)	3/12 6/12 12/12	UDVA,CDVA (LogMAR) UIVA, CIVA,DCIVA (66 and 80cm) UNVA, CNVA,DCNVA (33 and 40cm) Defocus (+1.00 to-4.00 (0.50steps)) Contrast Sensitivity (CSV-100) Ocular Aberations (OPD-Scan III)	
	AT LISA 839MP	Diffractve Trifocal +3.33Add	20					
Kaymak **2017**	AT LISA 801	Diffractive Bifocal +3.75Add	19	Bilateral	Yes(clinician) Unclear(subject)	1/12 3/12 6/12 12/12	UDVA,CDVA (LogMAR) UIVA, ,DCIVA (70,80, 90cm) UNVA ,DCNVA (40cm) Reading speed Defocus (+1.00 to -4.00)(0.50steps) Contrast Sensitivity (CSV-1000)	
	AT LISA 839MP	Diffractve Trifocal +3.33Add	16					
	AcrySof IQ Restor	Diffractive Bifocal +3.00Add	17					

UDVA unaided distance visual acuity, **CDVA** corrected distance visual acuity, **UIVA** unaided intermediate visual acuity, **UNVA** unaided near visual acuity, **CIVA** corrected intermediate visual acuity, **CNVA** corrected near visual acuity, **DCIVA** distance corrected intermediate visual acuity, **DCNVA** distance corrected near visual acuity

1.14.2 Comparison of outcome measures

Closer examination of the studies included in both recent reviews reveal the extent of the variation in outcome measures used (Table 1.3). This variability considerably limits the scope for intra-study comparison and precludes meta-analysis of pooled results (de Silva et al., 2016).

Table 1.3: Comparison of outcome measures

	Study	Visual Acuity	Reading Speed	Defocus	Questionnaire	Glare	Contrast Sensitivity	Other
2016	Cillino 2008	*		*	*	*[*]	*	
	El Maghraby 1992	*						
	Haaskjold 1998	*					*	
	Harman 2008	*	*	*	*	*[*]		*
	Javitt 2000	*			*	*[*]		
	Ji 2013	*					*	*
	Jusufovic 2011	*						*
	Kamlesh 2001	*		*	*		*	
	Labiris 2015	*			*	*[*]	*	
	Leyland 2002	*		*	*	*	*	
	Martinez Palmer 2008	*			*	*[*]	*	
	Nijkamp 2004	*			*			
	Peng 2012	*		*		*		
	Percival 1993	*					*	
	Rasp 2012	*	*					
	Rossetti 1994	*			*	*[*]	*	
	Sen 2004	*			*	*[*]	*	
	Steinert 1992	*		*	*		*	
	Wilkins 2013	*						
	Zhao 2010	*			*	*[*]	*	
2020	Mojzis 2014	*		*			*	*
	Jonker 2015	*	*	*	*		*	
	Cochener 2016	*		*	*	*[*]	*	
	Mojzis 2017	*		*			*	*
	Kaymak 2017	*	*	*			*	

Note: This refers to outcome measure only, not specific method of measurement
*[*] - glare assessed via questionnaire

With the exception of visual acuity there is no agreement on the outcome measures. Further, for some techniques e.g. defocus curves the method of analysis varied depending on the study and the IOL assessed. Wang was also unable to pool results in his review due to the

heterogeneity of outcome measures and methods of reporting (Wang et al., 2017). Sections 1.14.2.1 to 1.14.2.6 further explore the variations in methodology.

1.14.2.1 Vision and Visual Acuity

Although visual acuity (VA) was assessed in all studies and is typically a primary outcome measure, there were differences in not only the test type used but also variation in whether unaided or best corrected VA was measured, and indeed in the units of measurement, all of which make direct comparison between studies difficult.

1.14.2.1.1 Distance Visual Acuity

For distance assessment, some studies used Snellen charts at 6m (Cillino et al., 2008, el-Maghraby et al., 1992, Javitt and Steinert, 2000, Jusufovic, 2011, Kamlesh et al., 2001, Martinez Palmer et al., 2008, Percival and Setty, 1993, Sen et al., 2004, Zhao et al., 2010). In Javitt's study, despite measuring VA on a Snellen chart, the results were converted to LogMAR for analysis (Javitt and Steinert, 2000).Similarly, Jusufovic converted from Snellen acuity to decimal notation (Jusufovic, 2011). Early Treatment Diabetic Retinopathy Study (ETDRS) charts were used in others (Harman et al., 2008, Leyland and Pringle, 2006, Mojzis et al., 2014, Mojzis et al., 2017, Nijkamp et al., 2004, Peng et al., 2012, Rossetti et al., 1994, Wilkins et al., 2013). In the 2020 Review all studies used ETDRS charts and thus, LogMAR notation (Zamora-de La Cruz et al., 2020). In others it was not always clear from the study which method had been used (Rasp et al., 2012). Typically both unaided and best corrected visual acuity were measured.

1.14.2.1.2 Intermediate and Near Visual Acuity

There was no agreement on the method of near assessment; Sloan near charts, Jaeger near charts, Reagan charts and ETDRS charts were all used. Thus, there was no agreement on the use of single letters or sentence optotypes for reading assessment. The method of near assessment was not reported in all studies (Labiris et al., 2015), nor were testing distances consistent in all studies (Calladine et al., 2012, de Silva et al., 2016). Near visual acuity was measured from 33 to 50cm depending on study, and intermediate from 60 to 90cm. These disparities in methodology make comparison between studies difficult. In addition, near testing distance will be optimal if performed at the near focal point of the MIOL and thus in comparative studies could bias toward one MIOL.

These disparities in visual acuity methods have been recognised and uniformity called for (Williams et al., 2008). The ETDRS charts have been the gold standard of VA testing since their advent (Ferris et al., 1982, Williams et al., 2008). The addition of near charts following the ETDRS principles and LogMAR notation also now allows for standardisation of near and intermediate VA testing (Gupta et al., 2009).

1.14.2.2 Defocus

Defocus curves were plotted in almost half of the studies reviewed. Defocus curves are plotted by recording visual acuity across a range of imposed defocus. MIOLs show distinctive defocus curves. A peak is expected at each of the focal points of a given IOL (Maxwell et al., 2017). These peaks are dependent on design, one for a monofocal IOL, two for a bifocal and three for a trifocal IOL. They can provide important information regarding the range of clear vision achievable (Buckhurst et al., 2012b). In the 2016 Cochrane Review only seven studies plotted defocus curves, yet all did in the 2020 Cochrane Review (**Table 1.3**). This is perhaps a reflection

of the comparison lenses, researchers may assume that a defocus curve is of little informative value when comparing an MIOL to a monofocal, however it may simply be due to the small number included in the 2020 review, or indeed that defocus testing has become more popular in recent years.

1.14.2.2.1 Defocus Method

In those, who performed defocus assessment, there was variation, both with range of defocus assessed and the step size used. Cillino (Cillino et al., 2008) measured from +2.00 to -5.00D in 1.00D steps whereas Peng (Peng et al., 2012) used 0.50D steps. Leyland (Leyland et al., 2002) and Harman (Harman et al., 2008) both measured from +3.00 to -5.00D in 1.00D steps. Steinert (Steinert et al., 1992) measured defocus from +6.00 to -6.00D with varying increments. In addition to these varying ranges and increments, there was no agreement on the chart used, nor does any study report adjusting for back vertex distance (distance between the spectacle lens and they subjects eye). Methods for standardisation of measuring defocus curves have been proposed by Gupta (Gupta et al., 2007, Gupta et al., 2008). He concluded that standardised questioning and randomisation of letters presented was desirable. In addition, the order with which defocus is presented should be varied (i.e. not sequential) to avoid memorisation effects (Gupta et al., 2007, Gupta et al., 2008). A further study in 2013, investigated the optimal step size for defocus testing and concluded that valuable information could be lost with step sizes of 1.00D (Wolffsohn et al., 2013).

1.14.2.2.2 Defocus Analysis

In all studies, a direct comparison method was used. This provides a comparison of VA at each level of defocus, however metrics which provide an overview of the performance of the IOL

may be more informative (Buckhurst et al., 2012b). Buckhurst (Buckhurst et al., 2012b) proposed a method of defocus analysis that could differentiate between MIOLs, yet this has not been utilised in any of the RCTs reviewed that occurred after his method was published. His method requires a polynomial curve to be fitted to the data, it is possible that the difficulties incurred with curve fitting or clinician's inexperience with curve fitting may account for the reluctance to use such a metric. Thus, clarification of the curve fitting process required in defocus plotting may be of benefit and consequently increase uptake of this useful metric.

1.14.2.3 Reading Assessment

Near Visual acuity is the commonly measured reading metric measured in MIOL studies yet alternative measures such as reading speed or critical print size (smallest print that can be read while maintaining maximum reading speed) may align more closely with an individual's ability to perform near tasks (Gupta et al., 2009). Reading speed was only assessed in some studies using either the MN Read or Radner systems (Harman et al., 2008, Jonker et al., 2015, Kaymak et al., 2017, Rasp et al., 2012). Gupta advocates for the use of uppercase letter LogMAR charts, in addition to measuring critical print size and reading speed, also with LogMAR print in MIOL evaluations (Gupta et al., 2009).

1.14.2.4 Contrast Sensitivity

Contrast sensitivity was assessed in the majority of the studies, however again there were significant variations in methods used and the method of reporting. Pelli Robson charts, Functional Acuity Contrast Chart (FACT) charts, Vision Contrast Test System (VCTS), CSV-1000 and Regan charts were all used. This makes comparison between studies difficult (Calladine et al., 2012, de Silva et al., 2016, Leyland and Pringle, 2006). Zamora-de La Cruz recommended

that for future studies contrast sensitivity testing should be an outcome measure when reviewing bifocal and trifocal MIOLs. Forced choice test grating tests such as the CSV-1000 show low test reliability (Kelly et al., 2012). Reliability is greater with letter based charts such as the Pelli-Robson, but can be affected by literacy and there can be issues with illumination and test chart fading if paper charts are used (Richman et al., 2013).

1.14.2.5 Patient reported outcome measures

Patient reported outcome measures (PROMs) such as satisfaction and spectacle independence are important considerations in MIOL studies, particularly when spectacle independence has been the patient's motivating factor. It some studies, subjects were simply asked directly if they wore spectacles or not (Percival and Setty, 1993). In contrast, Martinez-Palmer's study assumed spectacle independence above a designated VA level (Martinez Palmer et al., 2008). In others, a questionnaire was used to assess satisfaction (Table 1.3). Those used were a mix of validated and non-validated questionnaires. Validated questionnaires have been appropriately tested to ensure applicability and high test-retest repeatability, thus the use of a validated questionnaire is preferable. The VF-7 (Uusitalo et al., 1999) was the most frequently used questionnaire (Cillino et al., 2008, Rossetti et al., 1994, Sen et al., 2004, Steinert et al., 1992, Zhao et al., 2010). It is a modified version of the VF-14 questionnaire which was used also (Labiris et al., 2015, Nijkamp et al., 2004). The VF-14 was designed to be used in cataract surgery and makes no reference to visual disturbances such as halos and glare (Steinberg et al., 1994). Other validated questionnaires are available but are specific to certain aspects of patient satisfaction only. The NAVQ (Buckhurst et al., 2012a) addresses satisfaction with near tasks only and there are questionnaires directed toward visual quality and visual disturbances (Aslam et al., 2004a, Aslam et al., 2004b, McAlinden et al., 2010).

1.14.2.6 Halos and Glare

Photic phenomena (halos and glare), otherwise known as dysphotopsia, in MIOLs is an accepted occurrence (Woodward et al., 2009). The majority of the studies where the occurrence of halos and glare was assessed did so in the form of a questionnaire, typically using a Likert grading scale (Cillino et al., 2008, Harman et al., 2008, Javitt and Steinert, 2000, Labiris et al., 2015, Martinez Palmer et al., 2008). In contrast, other studies used the BAT (brightness acuity tester) glare disability assessor (Marco Ltd, Jacksonville, FL, USA) (Leyland et al., 2002) and the C-Quant straylight meter (Oculus, Wetzlar, Germany)(Peng et al., 2012). In the 2020 Cochrane Review, only Cochener used a questionnaire to evaluate dysphotopsia(Cochener, 2016). Both studies by Mojzis used the OPD-II scan (Nidek, Japan) to assess ocular aberometry but did not directly address dysphotopsia subjectively (Mojzis et al., 2014, Mojzis et al., 2017).

The photopic scotoma size of a central glare source can be measured by devices known as halometers (Buckhurst et al., 2017, Buckhurst et al., 2015, Meikies et al., 2013). The Aston halometer is able to differentiate patterns of dysphotopsia generated by differing MIOLs that are not apparent with straylight measures (Buckhurst et al., 2017).

It is clear there is no agreement either on outcome measures to be included nor in the equipment/methods used to perform clinical measures. In addition, there is variation in the testing distances used, especially for near assessment and whether these assessments are carried out unaided or with spectacle correction and monocular or binocular.

1.14.3 Comparison of study intervals

When the individual studies from the 2016 and 2020 Cochrane reviews were compared, there was considerable variation in the post-operative interval for assessment and the number of assessments (**Table 1.4**) (de Silva et al., 2016, Zamora-de La Cruz et al., 2020). The majority of studies (16 of 25) evaluated subjects at 6 months or less post-operatively. Of the 25 studies, 14 only evaluated subjects at 1 visit, the remainder included 2-5 visits. The studies with more than one study visit, did not always perform all assessments at each visit (Jonker et al., 2015, Kaymak et al., 2017, Martinez Palmer et al., 2008, Mojzis et al., 2017).

Table 1.4: Comparison of post-operative interval

Study		Months					
		< 1	1-2	2-3	3-6	7-12	13-18
2016	Cillino 2008	*	*	*	*	*	
	El Maghraby 1992		*	*			
	Haaskjold 1998				*		
	Harman 2008			*			*
	Javitt 2000			*			
	Ji 2013	*	*	*			
	Jusufovic 2011		*				
	Kamlesh 2001	*	*	*			
	Labiris 2015					*	
	Leyland 2002			*		*	*
	Martinez-Palmer 2008	*	*	*			
	Nijkamp 2004			*			
	Peng 2012	*	*		*		
	Percival 1993				*		
	Rasp 2012						*
	Rossetti 1994			*	*	*	
	Sen 2004		*				
	Steinert 1992			*			
	Wilkins 2013				*		
	Zhao 2010	*	*			*	
2020	Mojzis 2014			*			
	Jonker 2015		*	*	*		
	Cochener 2016				*		
	Mojzis 2017			*	*	*	
	Kaymak 2017		*	*	*	*	

Note: 2020 Review only included trials with a minimum of 3 month follow up

Wang highlighted the need for longer term follow-up to ensure that adverse outcomes such as IOL exchange due to patient dissatisfaction can be evaluated (Wang et al., 2017). In 2016 Rosen initiated a systematic review of MIOL studies, not confined to RCTs (Rosen et al., 2016). He included 126 published studies. They commented on the variation in follow up intervals and its effect on the assessment of outcome measures such as halos and glare and contrast sensitivity which are known to improve with time (de Vries et al., 2011, Kohnen et al., 2009, Mester et al., 2007, Montes-Mico et al., 2004, Sood and Woodward, 2011) . This is thought to be due to neuroadaptation (Rosa et al., 2017a, Rosa et al., 2017b). This would suggest that studies should include at least two post-operative visits, a short term and a longer term visit in order to fully assess the visual function over time.

1.14.4 Discussion

Section 1.14 has only explored the differences in methodology between those studies included in Cochrane reviews pertaining to MIOLs. It has not assessed the plethora of cohort studies available in detail. This reflects the position of systematic reviews and RCTs over cohort studies on the hierarchy of evidence. In addition to the Cochrane reviews there have been a number of additional systematic reviews, with very similar conclusions. This is not surprising as there is considerable overlap with the studies included in each of these reviews. Despite the recommendations of the 2016 Cochrane review, we could only identify one new RCT including a monofocal control group (Maxwell et al., 2017) in the subsequent years. There still remains a paucity of RCTs comparing MIOLs to their monofocal counterparts, particularly in recent years despite the advances in MIOL designs.

A core set of outcomes has been proposed by Evans in recent months (Evans et al., 2020). They suggest that distance visual acuity, near visual acuity, contrast sensitivity, both unaided and

corrected are recorded in all MIOL studies as a minimum. They also recommend questionnaires be used to assess spectacle independence, quality of life and the occurrence of halos and glare. Their proposal is based on the studies from the 2016 Cochrane Review and their assessment of those outcome measures as most studies reported distance and near visual acuity, contrast sensitivity and PROMs in some format. However, this minimum dataset proposal fails to include intermediate vision or defocus profiles. Although they specify the use of LogMAR charts for distance and near assessment, they do not specify a working distance and in the absence of defocus profiles this could bias results. Rosen also highlighted the variations in working distance used and advocates for the assessment of defocus profiles in MIOL studies (Rosen et al., 2016). Previous literature has called for standardisation for defocus methods and reporting (Buckhurst et al., 2012b, Gupta et al., 2007), yet Rocha-de-Lossada (Rocha-de-Lossada et al., 2020) has recently commented on the lack of standardisation that still remains. There is considerable disparity in the methods for interpreting defocus data, if a direct comparison at each defocus interval is considered only, this still leads to difficulty in comparison between studies, unless the same intervals are applied. It also may bias toward MIOLs of particular addition powers. Buckhurst's (Buckhurst et al., 2012b) method providing a global overview would minimise this bias, however in order to increase uptake of such a metric, clarity on the curve fitting process and analysis is required.

The Evans report suggest a follow up interval of between 6 and 18 months (Evans et al., 2020). Longer term follow up was also recommended by Wang and Rosen (Rosen et al., 2016, Wang et al., 2017). The evidence for neuroadaptation (Rosa et al., 2017b) and the subsequent improvement to outcomes reported in the literature such as dysphotopsia, contrast sensitivity and reading performance further support the need for long term follow up in studies involving MIOLs (Anton et al., 2014, Goes, 2008, Kohnen et al., 2009, Mester et al., 2007, Montes-Mico and Alio, 2003, Montes-Mico et al., 2004, Sood and Woodward, 2011). Rosa's work on

neuroadaptation found increased cortical activity in subjects with a MIOL (Rosa et al., 2017b). This increased activity was in areas related to task processing, and the activity had reduced when reassessed at 6 months following implantation, in addition to improvement in subjective quality of vision questionnaire scores (Mukai et al., 2007, Rosa et al., 2017b). Neural processing is known to increase with repetition of a task and as such the task becomes easier with time (Lewis et al., 2009). The brain becomes attuned to the relevant features of a task and thus can extract the information with increasing fluency (Kellman and Garrigan, 2009). Therefore, if MIOL studies are only conducted at < 6 months post-operatively, they may not give a true reflection of the visual performance of MIOLs once an individual has adapted.

The reviews highlight the need for further studies to (a) investigate the relative effectiveness of current MIOLs for the management of presbyopia following cataract surgery or refractive lens exchange (b) develop a core set of outcome measures for assessing MIOL and to facilitate comparisons across studies.

1.15 Conclusion

Premium intraocular lens development is constantly evolving, and there are many differing IOL designs now available to surgeons, yet there has been little change in the way that the clinical outcomes of such IOLs are investigated. Despite the wealth of studies that have been published for MIOLs and TIOLs, comparison of the literature can be difficult due to the variety of methodologies used. Cochrane Reviews have highlighted a need for further randomised control trials and calls for standardisation of outcome measures and methodology to allow comparison between studies in the future. In addition, follow up interval must be sufficient to establish function following neuroadaptation. Further investigation of outcome measures is

required and analysis of the most appropriate methods/devices to use to assess parameters. Often the device or chart used will be dependent on the clinical setting and it may not be practical nor feasible to suggest that future MIOL studies must adhere to an overly restrictive protocol, yet standardisation of basic measures such as visual acuity testing with LogMAR notation would significantly improve comparability of studies In addition, it must be recognised that visual acuity is insufficient as an isolated measure to report MIOL outcomes. As such, defocus profiles can be a vital tool. Previous literature has demonstrated detailed metrics for analysis of defocus curves, yet there is no agreement on the curve fitting technique essential to allow standardisation of such a method and this warrants further investigation. In addition, to VA testing and defocus, contrast sensitivity patient reported outcome measures should be included in MIOL studies as they provide a vital insight to visual function post-operatively.

Near performance is of upmost importance in presbyopic corrections, and VA testing, defocus analysis and PROMs can assess the near visual performance. However, despite the knowledge that the labelled addition powers of an MIOL does not detail the power at the spectacle plane, there has been little investigation of the post-operative addition power achieved in individuals and whether this can be predicted with IOL power formulae as we would for distance outcomes. Pre-operative prediction of addition power can only be beneficial in choosing the most appropriate MIOL for an individual's needs.

The detrimental effect of uncorrected astigmatism to visual acuity has been reported, and it is known that toric intraocular lenses can provide correction of astigmatism, yet rotational stability and refractive outcomes of TIOLs require further investigation. The rigorous investigation using vector analysis and digital imaging is advocated to fully understand post-operative results and thus allow meaningful comparison of TIOLs.

Therefore, the aims of this thesis are:

a) To investigate the effectiveness of premium IOL implantation

b) To use rigorous and repeatable methodology to evaluate premium IOLs in a move towards standardisation of outcomes

The aims of the thesis will be achieved through the following objectives:

- To explore the methods of curve fitting for defocus data to allow future comparison of MIOL designs using detailed defocus metrics (Chapter 2)

- To evaluate a simple clinical method for predicting post-operative near addition power at the spectacle plane in MIOLs (Chapter 3)

- To conduct a rigorous RCT comparing multifocal and monofocal IOLs using a robust and detailed methodology (Chapter 4)

- To compare long term outcomes in multifocal IOLs (Chapter 5)

- To assess the rotational stability and refractive outcomes of closed loop and plate haptic toric IOLs in an intra-patient randomised control trial (Chapter 6)

Chapter Two

Optimising curve fitting techniques to enable standardised analysis of defocus curves: An exploratory study

OVERVIEW

Defocus Profiles are a useful method when comparing multifocal IOLs, however there is currently considerable variability in the methods utilised for analysis of defocus data.

Using a previous published data collection method and analysis metric, this study aimed to add further clarity and standardisation to the methodology by exploring curve fitting techniques.

Polynomial curves from 2^{nd} to 11^{th} order and a cubic spline curve were fitted to defocus data (+1.50D to -5.00D) from five different IOL designs and five curve fitting strategies were examined

There was no agreement between polynomial orders and thus the cubic spline was found to be the most appropriate fit in all IOLs.

2.1 Introduction

With such a wide variety of MIOLs available, comparison of such lenses can be difficult. Although many different lenses may be grouped together as MIOLs, their characteristics vary greatly, in both design and addition power, as outlined in Chapter 1. MIOLs generate multiple focal points within the eye extending the range of clear vision achieved post cataract surgery. Due to these differences in design and addition power, the range of clear vision achievable post implantation may differ between MIOLs. Clinicians must fully understand the optical characteristics of individual MIOLs in order to appropriately counsel patients considering implantation. Patient preferred reading distance and lifestyle are important considerations in presbyopic correction (du Toit, 2006). Such an understanding allows selection of the MIOL best suited to a patient's visual requirements, thus maximising patient satisfaction. Despite the extensive published literature on MIOLs, not all studies employ the same methods and in particular the assessment of near and intermediate vision varies greatly between studies (de Silva et al., 2016). The ability, to directly compare the optical performance of differing MIOLs can be challenging. A MIOL with reading addition of +2.50D in the spectacle plane, will perform optimally if near acuity is assessed at 40 cm, however this would be less favourable for an MIOL with a +3.50D addition power. To avoid preferential testing conditions for one or more IOLs in comparative studies, the assessment of acuity at varying distances is required. However, measuring visual acuity (VA) physically over a range of distances is largely impractical due the difficulties that can arise in controlling target illuminance and angular size (Pieh et al., 2002). Therefore, defocus curves are often plotted to assess the functionality of an MIOL and its ability to provide a range of vision (Buckhurst et al., 2012b, Cillino et al., 2008).

2.2 Defocus Curves

Defocus curves are plotted by recording visual acuity across a range of imposed defocus. MIOLs have at least 2 distinct focal points and as such show a distinctive defocus curve profile, with peaks in acuity corresponding to the distance, intermediate and/or near focus (Maxwell et al., 2009). A standardised methodology must be used, otherwise independently selected step sizes or reduced defocus range may inadvertently bias results toward a single MIOL (Gil et al., 2019, Pedrotti et al., 2018, Plaza-Puche and Alio, 2016). Thus, it is essential to minimise bias when analysing defocus curves. There is a diverse array of metrics that can be used to analyse defocus curves.

2.2.1 Direct Comparison

The direct comparison method is the most widely used in the literature (Gil et al., 2019, Pedrotti et al., 2018, Plaza-Puche et al., 2015, Plaza-Puche and Alio, 2016, Savini et al., 2018b). This method of comparison requires analysis of VA at each level of defocus; however, since these measures are inherently linked this needs to be accounted for statistically to avoid clinical misinterpretation (Bland and Altman, 1986, Buckhurst et al., 2012b, Gupta et al., 2008). Direct comparison only describes the performance of an IOL at arbitrary levels of defocus, for example -2.00 and -2.50 defocus. This may bias for or against specific IOLs and there is no agreement in the literature which defocus levels are considered most important (Gil et al., 2019, Pedrotti et al., 2018, Plaza-Puche and Alio, 2016). Thus, metrics which give an overview of the MIOL performance may be more informative.

2.2.2 Depth of Focus

An alternative method for analysing defocus curve data, considers depth of focus(DoF). Depth of focus (DoF) is considered the distance in front and behind the retinal focal point over which an image can be focused without causing a reduction in clarity beyond an acceptable level (Milodot, 2018). Depth of field is the distance over which an object can be moved without a reduction in clarity beyond an acceptable level (Milodot, 2018). For defocus curves, depth of focus is the usual terminology but often these terms are used interchangeably. There are both, the absolute and the relative depth of focus methods to be considered (Buckhurst et al., 2012b, Gupta et al., 2008, Kuchle et al., 2004, Sauder et al., 2005). These RoF methods calculate the dioptric range over which participants can maintain a specified chosen level of VA. With the relative depth of focus criterion, the cut-off VA is relative to the best corrected visual acuity, the more commonly used absolute depth of focus method involves an absolute VA cut off that is independent of best corrected VA. To date there is no agreed standard of VA that is employed throughout the literature (Buckhurst et al., 2012b, Gupta et al., 2008). However, 0.3LogMAR is typically used as a cut off value, as this is the visual driving standard in many countries (Bron et al., 2010, Rees, 2015). Furthermore, studies where depth of focus metrics have been used, have not always specified the VA criterion used, nor have they addressed how sections within the total dioptric range that fall below the cut off are accounted for/excluded from the dioptric range (Kamlesh et al., 2001, Leyland et al., 2002). Some authors (Buckhurst et al., 2012b, Gupta et al., 2008) have advocated fitting a curve to the data and thereafter using the Newton-Raphson method to find x when $y = 0.3$ (where x = level of defocus, and y = visual acuity) and thus every intersection of the curve at 0.3LogMAR in order to account for these issues (Ypma, 1995).

2.2.3 Area of Focus

The area of focus (AoF) metric, proposed by Buckhurst, advocates dividing the defocus curve into 3 sections: Distance +0.50D to -0.50D, Intermediate -0.50D to -2.00D (50cm to 2m) and Near -2.00D to -4.00D (25cm to 50cm) (Buckhurst et al., 2012b). This method considers the actual VA within the range, not just whether VA is better or worse than a set criteria. This method of defocus analysis requires a curve to be fitted to the data and the curve integrated so the AOF metric (LogMAR*m^{-1}) can be derived. It also utilised a 0.3LogMAR cut-off value, in accordance with the aforementioned published standards (Bron et al., 2010, Rees, 2015). The area sections; distance, intermediate and near, in combination with the cut-off value define the limits of integration. In comparison to the relative and absolute depth of focus methods, Buckhurst's method is advantageous in its ability to compare lenses over a range of defocus rather than individual points of the direct method, removing some of the inherent bias of toward MIOLs with add powers best suited to the arbitrary defocus intervals. It was also able to differentiate between MIOL designs, whereas relative and absolute depth of focus methods did not (Buckhurst et al., 2012b).

Irrespective of the differences in how the RoF and AoF metrics are calculated, they are both dependent on the optimal curve fitting of the defocus data, however, no prior study has examined the optimal method for fitting a curve to this type of data and the majority of studies fail to report on the type of curve fitted.

2.3 Curve Fitting

Curvilinear regression (fitting a curve), finds a mathematical expression that produces a curved line to be the closest or exact fit to the measured data points, when the relationship between

variables is non-linear (McDonald, 2014). The validity of this curvilinear regression should be assessed statistically. This analysis is commonly referred to as goodness of fit (GoF), and describes how well the curve fits the data.

There are many benefits in fitting a curve to raw data, it allows interpolation and extrapolation of the data. It also allows visualisation of data that can aid establishing relationships.

2.3.1 Polynomial Curves

The Oxford dictionary defines a polynomial as an expression consisting of two or more terms, more specifically in mathematics, two or more algebraic terms, particularly a function which includes the sum of differing positive powers of the same variable.

A 1st order polynomial function is defined as $y = a_0 + a_1 x$

A 2nd order polynomial function $y = a_0 + a_1 x + a_2 x^2$

A *n*th order polynomial function $y = a_0 + a_1 x + a_2 x^2 \ldots\ldots\ldots\ldots a_n x^n$

Equation 2.1: Polynomial Functions

The maximum order polynomial that can be fitted to a data set (n) is of *n-1* order. A 1st order polynomial will provide an exact fit for 2 data points in the series, a 2nd order will pass exactly through 3 data points in a series. If a high order polynomial is used it is possible to get almost an exact match to the data set, however there are several reasons why a lower order and approximate fit are a better option. Using a lower order polynomial allows “averaging out” of

questionable data in the series, whereas higher order polynomial pass through most points, depending on the order. Higher order polynomials are also subject to Rungé phenomena, oscillations that occur at the end points of a curve when polynomial interpolation was performed using equally spaced data points (Runge, 1901). In order to establish the presence of Rungé phenomena, visual inspection of the curves must be performed.

2.3.2 Spline Curves

A spline curve is a mathematical function defined piecewise by polynomials. These are complex curves often used in industry to define surfaces that cannot easily be represented with simple curves such as circles or ellipses (Bartels, 1998) . Interpolated spline curves pass through all data points. A cubic spline uses 3^{rd} order polynomials between the data points (Bartels, 1998). Using only lower order polynomials avoids the issues of Rungé phenomena.

2.3.3 Current curve fitting practices

In previous literature relating specifically to defocus curves, rarely is curve fitting detailed. Of the few reporting, there is a significant discrepancy in the methods used. Gupta (Gupta et al., 2008) used 5^{th} to 10^{th} order polynomials , whereas Buckhurst (Buckhurst et al., 2012b) used a 9^{th} order polynomial, and Wolffsohn (Wolffsohn et al., 2013) used a spline curve in his investigation of optimum step size in defocus measurement (Wolffsohn et al., 2013). Gupta and Buckhurst differed in their statistical assessment of GoF (Buckhurst et al., 2012b, Gupta et al., 2008). The former chose polynomial order based on highest possible regression coefficient (R^2) achievable and visual inspection, whereas the latter selected a 9^{th} order polynomial based on no noticeable further improvement to R^2 nor further decrease in standard error (Buckhurst et al., 2012b, Gupta et al., 2008). By nature, adding a higher order term will always increase R^2,

but an increase in R^2 is only relevant if it is significantly greater than that expected due to chance. (McDonald, 2014) Thus, reliance on R^2 alone seems insufficient evidence to advocate either of these methods in future studies. Petermeier used the least squares method to assess GoF in their studies; however, they do not report which order polynomial was the best fit to the data (Petermeier et al., 2011).

Polynomials are relatively simple mathematical expressions and thus are clinically accessible given the ease with which they can be solved and integrated to facilitate the generation of DOF and AOF metric values. In comparison, a spline curve, as used by Wolffsohn (Wolffsohn et al., 2013) is guaranteed to pass through all data points but requires more complex mathematical modelling to generate the desired metric values.

We must understand what curve to use to maintain consistency in the evaluation of defocus curve and to utilise range of focus/ area of focus metrics appropriately.

However, to date, there is no consensus between studies, on neither which curve to fit, nor which criteria should be used to assess GoF. The literature describes many methods for analysing GoF (Akaike, 1974, Anderson-Sprecher, 1994, Draper, 1998, Snedecor, 1967, Stigler, 1981, Yang L, 2008) yet there is no established method in the context of defocus data.

Therefore the aims of this study are:

- To establish the most appropriate GoF method for defocus curve fitting
- To establish the most appropriate curve to use with differing IOLs
- To determine if a single polynomial function can fit a variety of MIOLs and EDoF defocus curves to an equivalent standard as a spline curve.

2.4 Study Design

This prospective cohort study recruited participants undergoing bilateral phacoemulsification and IOL implantation with one of five different IOLs at the BMI Southend Hospital. Participants were recruited from routine cataract or refractive lens exchange clinics. All participants gave written informed consent. The study adhered to the tenets of the Declaration of Helsinki and received ethical approval from the University of Plymouth Ethics board on 19th May 2014 (13/14-239) (Appendix 1).

2.4.1 Participants

All participants met the inclusion/exclusion criteria outlined in Table 2.1 below. One hundred and twenty six participants were recruited.

Table 2.1: Inclusion/Exclusion Criteria

Inclusion	Exclusion
Participants requiring primary IOL implantation	Subjects with retinal pathology
Participants with a potential corrected visual acuity of 0.3 LogMAR or better on clinical assessment in both eyes	Previous intraocular and/or corneal surgery
Subjects with clear intraocular media and normal anterior segment other than cataract	Subjects using a systemic medication that is known to cause ocular side effects
Participants aged 18+ years	Pregnant women
< 1.00D of preoperative corneal astigmatism	Subjects who could not make an informed consent

2.4.2 Intraocular Lenses

The five groups of patients were bilaterally implanted with either the Bi-Flex 677AB Monofocal IOL, Bi-Flex MY diffractive bifocal IOL, Oculentis Mplus refractive bifocal, AMO Symfony Extended Depth of Focus IOL, and the AT LISA 839MP diffractive trifocal IOL (Table 2.2).

Table 2.2: Study IOLs

	Bi-Flex 677AB	Bi-Flex MY	Mplus	Symfony	AT LISA 839
Design	Monofocal	Diffractive Bifocal	Refractive Bifocal	EDoF	Diffractive Trifocal
Add Power	N/A	+3.50D	+3.00D	N/A	+3.33D
Subjects	28	30	25	18	25

2.5 Surgery

All surgeries were performed by one of two experienced consultant ophthalmic surgeons (RA and HK). The same surgeon implanted both eyes of a given subject.

2.5.1 Surgical Technique

Surgery was performed by small incision phacoemulsification as detailed in Section 1.5.4, using topical anaesthetic (Minims®Proxymetacaine hydrochloride 0.5% (Bausch & Lomb)) and a 2.2mm clear corneal incision located on the steepest corneal meridian. The OVD used was Hydroxypropyl Methylcellulose (HPMC). During surgery, 1% cefuroxime was instilled intracamerally.

2.5.2 Post-Surgical Medication and Advice

Following surgery, the subjects were instructed to use Tobradex 3mg/ml/1mg/ml (Novartis) four times daily for four weeks following surgery. Standard post-operative advice was provided verbally and as an information leaflet.

2.5.3 Post-Operative Visit

Following surgery to their first eye, the subject was requested to attend routine post-operative consultation within one week of surgery. If no complications were identified then the subject was given a surgical date for the second eye within 3 weeks. Following second eye surgery the subject was asked to return for follow up 4 weeks post-surgery. Providing there were no complications at 4 weeks, the subject was asked to return for a study visit 3-6 months post-operatively.

2.6 Method

At 3-6 months, subjects returned for further assessment. Visual acuity was assessed binocularly on the Thomson Test Chart 2000 (Thomson Software Solution, Hatfield, Herts, UK) at 6m. The same optometrist carried out manifest subjective refraction to establish best distance correction. All tests were performed in photopic conditions of illuminance 120 cd/m2 and luminance of 95 lux.

2.6.1 Defocus Profiles

Defocus curves were plotted once for each subject binocularly with best distance refractive correction in place, with defocus ranging from +1.50D to -5.00D in 0.50D steps in accordance with previously published methodology (Wolffsohn et al., 2013). In accordance with the methods described by Gupta (Gupta et al., 2008), the presentation of both letters and lenses were randomised to avoid any learning effects. The participants were prompted once by the phrase of "can you read any more letters on the line below?" in order to standardise the level of encouragement throughout the test (Gupta et al., 2007). In addition, a mathematical correction for spectacle magnification (Gupta et al., 2008) must be employed to limit underestimation of VA with this method (Equation 2.2).

The defocus curves were plotted with the standard 14 data points and best fit polynomial regression curves from 2^{nd} to 11^{th} order were fitted using SigmaPlot Version 13 (Systat Software Inc, San Jose, CA, USA)(Figure 2.1) and MATLAB R2017b (The Mathworks Inc, Natick, MASS, USA. The fitting process was limited to 200 iterations for each curve as recommended by SigmaPlot curve fitting programme. In addition, cubic spline curve, composed of piecewise third order polynomials, was fitted to the data. An example of the curves fitted for an individual subject as illustrated in Figure 2.1.

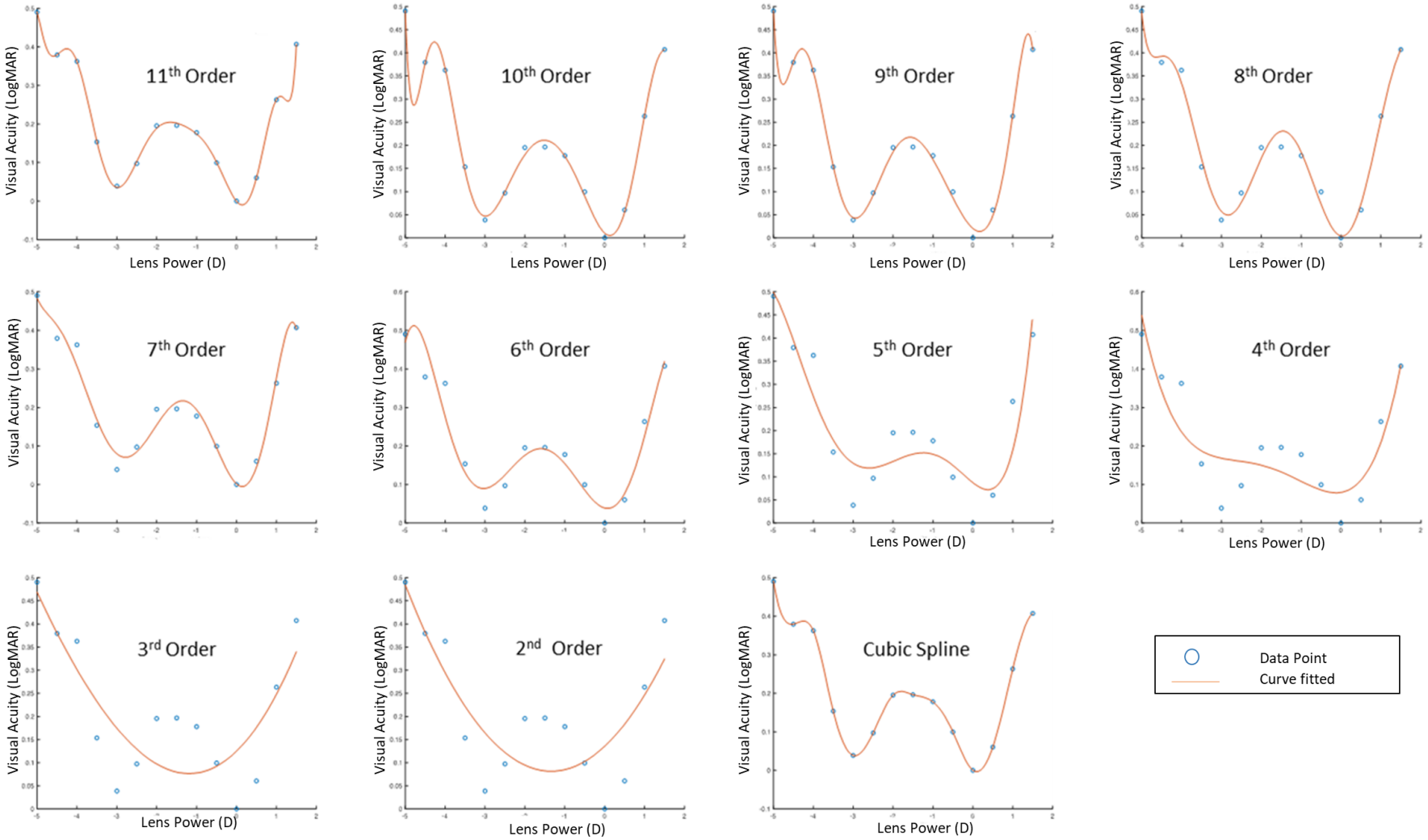


Figure 2.1: Example of curve fitting in an individual bifocal subject

Additionally, VA measurements for defocus of -2.25D and -2.75D were obtained in the monofocal and bifocal group for the purpose of validation, further discussed in Section 2.7.2.

2.7 Statistical analysis

Statistical analysis was performed using SPSS Version 24 (SPSS Inc, IBM, Armonk, NY, USA) and SigmaPlot Version 13 (Systat Software Inc, San Jose, CA, USA). Results were tested for normality using the Kolmogorov-Smirnov test (p >0.05), thereafter parametric tests were used as the data followed a normal distribution. In all instances p <0.05 was considered statistically significant.

2.7.1 Spectacle Magnification

When refractive lenses are placed in front of the eye, there is a magnifying effect on the retinal image, this effect is dependent on the power of the spectacle lens, the distance of the lens from the eye (back vertex distance (BVD)) and its refractive index (Gupta et al., 2008). All defocus data was corrected for spectacle magnification (SM) assuming a thin lens calculation with back vertex distance (BVD) of 12mm (Equation 2.2).

$$SM = \frac{1}{1 - dF}$$

SM = spectacle magnification
d = back vertex distance
F = lens power

Equation 2.2: Spectacle magnification for a thin lens

2.7.2 Analyzing goodness of fit

The following five models for analysing curve fitted were used in all subjects in order to assess goodness of fit and thus determine the most appropriate polynomial(s).

1. Least Squares
2. Coefficient of determination (R^2)
3. Akaike Information Criterion (AIC)
4. Snedecor & Cochrane Method
5. Visual Inspection

2.7.2.1 Least Squares

The Least Squares method of curve fitting finds the curve which best represents a data set, such that the sum of square of the vertical distance from each data point to the line is a minimum (Stigler, 1981). This provides an F statistic, a ratio of the variance in the dependent variable as a function of the independent variable and the residual deviation from the curve. A large F statistic, suggests a curve with a good fit to the data.

$$F = \frac{mean\ square\ (model)}{mean\ square\ (residual)}$$

Equation 2.3: Least Squares F statistic

2.7.2.2. Coefficient of determination (R^2)

The coefficient of determination is the ratio of variance explained by the model (curve) to total variance (Anderson-Sprecher, 1994, Draper, 1998). It considers the proportion of the variance in the dependent variable that is predictable from the independent variable. An R^2 equal to 1 shows that the curve perfectly fits the data points. The coefficient of determination will always increase as more variables are added to a model and as such overfitting can occur, with a deceptively high R^2 achieved (Anderson-Sprecher, 1994). Thus, we have chosen to use the adjusted R^2 (R^2_{adj}), this includes an additional calculation to adjust for the number of variables included in the curve fitting. As such the R^2_{adj} will increase only if the increase in R^2 by the addition of an extra term is more than can be explained by chance.

2.7.2.3 Akaike Information Criterion (AIC)

Akaike Information Criterion (AIC) is an estimator of the relative quality of statistical models for a given dataset. When various models are used, AIC estimates the quality of each model, relative to the other model by estimating the relative information lost by a given model (Akaike, 1974). The less information lost, the higher the quality of the model. In order to estimate information lost, AIC assesses the trade-off between goodness of fit and the simplicity of the model. Thus, the lower the AIC, the better the model.

$$AIC = 2K - 2\ln L$$

K = number of parameters
L = maximum value of the likelihood function

Equation 2.4: Akaike Information Criterion

When the sample size is small, as in this study, it is likely that AIC will overfit, thus AICc is used and employs a correction factor for a small sample size (Akaike, 1974).

$$AIC_c = AIC + \frac{2K^2 + 2K}{n - K - 1}$$

n = sample size

Equation 2.5: Small sample Akaike information criterion

2.7.2.4 Snedecor & Cochrane Method

Snedecor & Cochrane describe a method to analyse curve fitting in order to minimize the risk of overfitting (Snedecor, 1967). It aims to find the minimum order (least complex equation) that can be fitted and gives a significant improvement to the sum of squares of the regression. An F statistic is calculated by assessing the change in sum of squares between the higher order curve and the previous order, to see if the increased order has provided a significant improvement.

2.7.2.5 Visual Inspection

All plotted curves were assessed visually and the same observer made a determination of the best fit. A fit was considered poor if certain issues were observed, e.g. “over fitted” if there were additional inflection points, known as Rungé phenomenon (Runge, 1901), observed at the extremes, or “under fitted” if there was no inflection observed in the intermediate or near areas as expected.

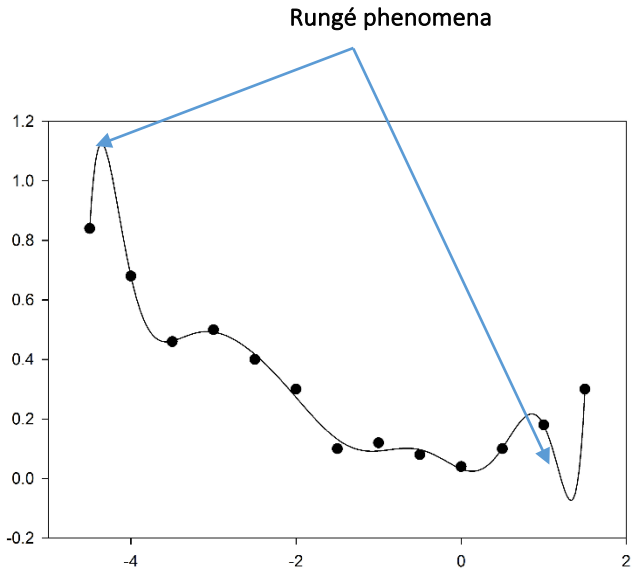


Figure 2.2: Example of Rungé phenomena

2.7.3 Validation

In addition, VA measurements for defocus of -2.25D and -2.75D were obtained in the monofocal and bifocal group for the purpose of validation; these additional points were excluded from the initial curve fitting process. These values were chosen as the correspond with the expected near area of the bifocal IOL and thus most likely to highlight the near inflection points.

The fitted curves were used to interpolate the y value (VA) when χ (defocus) was -2.25D and -2.75D. The results of these predictions were compared to the actual measured values. As part of this validation exercise, the same software (MATLAB 2017b, The Mathworks Inc, Natick, MA, USA) was used to calculate the area under the curve (LogMAR*m^{-1}) and range of focus assuming a ceiling of y = 0.3 LogMAR using previously published methodology (Buckhurst et al., 2012b).

Repeated measure ANOVA and post *hoc* Bonferroni test was used to compare the means for validation data points

2.7.4 Defocus Metrics

A two-way repeated measures ANOVA for Area Distance, Area Intermediate, Area Near, Total Range of Focus and Actual Range of Focus was calculated. In addition, Pearson's Correlation and Bland Altman (Means vs difference) plots were used to test the limits of agreement (Bland and Altman, 1986).

2.8 Results

All one hundred and twenty six subjects completed the study and good distance visual acuity (>0.20LogMAR) was measured in all. (Figure 2.3).

Table 2.3: Patient Demographics

	Bi-Flex 677AB Monofocal	Bi-Flex MY Bifocal	Mplus	Symfony	AT LISA Trifocal
Age	77.68 ± 5.20	76.53 ± 6.75	62.57 ± 8.24	62.67 ± 12.98	67.76 ± 7.50
Sex	10 male 18 female	6 male 24 female	9 male 16 female	7 male 11 female	7 male 18 female

Mean years ± standard deviation

Mean defocus data for each of the 5 IOLs was plotted, in order to establish defocus patterns (Figure 2.3). It can be seen from the plots that differences are apparent visually between the

groups. However, crude visual inspection also indicates similarities between the monofocal and EDoF profiles. In addition the remaining MIOLs have similarities in the shapes of their profiles also.

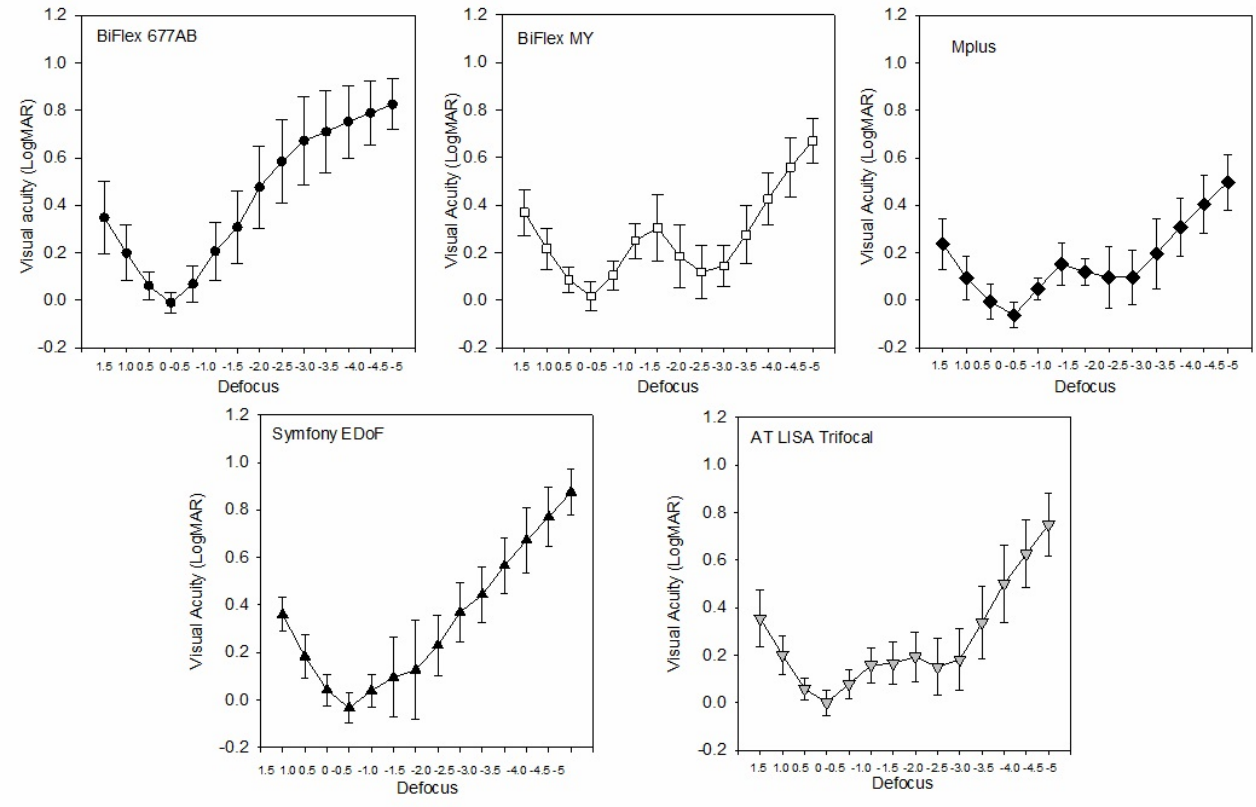


Figure 2.3: Mean defocus profiles. Error bars =standard deviation

Table 2.4 outlines the best fit polynomial as determined by each of the statistical methods. Least squares and R^2_{adj} tend towards higher order curve fitting, whereas AICc and Snedecor & Cochrane methods suggest lower order polynomials are sufficient to fit all the IOLs.

Table 2.4: Comparison of Curve fitting methods					
	Least Squares	R^2_{adj}	AICc	Snedecor & Cochrane	Visual
Bi-Flex 677AB	7^{th}	5^{th}	3^{rd}	2^{nd}	3^{rd}
Bi-Flex MY	9^{th}	8^{th}	4^{th}	2^{nd}	7^{th}
Mplus	9^{th}	8^{th}	2^{nd}	2^{nd}	7^{th}
Symfony	10^{th}	4^{th}	2^{nd}	2^{nd}	3^{rd}
AT LISA 839	11^{th}	7^{th}	2^{nd}	2^{nd}	7^{th}
Data = polynomial order					

Only the Snedecor & Cochrane method was consistent across all IOLs, however from visual inspection it was clear that this constituted under fitting in the MIOLs and important information in the intermediate and near sections of the defocus profile would be lost (Figure 2.1). Generally, visual inspection indicates in the bifocal/trifocal lenses that higher order curves are required to avoid missing the intermediate and near inflection points of the defocus profile in MIOLs but lower order curves would suffice in the monofocal and EDoF. Least square indicates a minimum of a 7^{th} order polynomial is required to fit the monofocal group, and higher order still for the remaining lenses, yet all other methods suggest a lower order polynomial. It appears that the least squares method is the least conservative and most likely to lead to overfitting.

Otherwise there was no agreement between methods for polynomial order, nor was there consistency in methods for individual lenses.

The validation analysis examined fifty-eight (58) participants (30 Bi-Flex M and 28 Bi-Flex 677 AB) and compared the VA for defocus of -2.25 and -2.75, to the VA interpolated from the curves fitted to the defocus data. Comparison of the mean VA by repeated measures ANOVA revealed significant differences in the bifocal group for both -2.25D (F_{10} =13.653, $p < 0.01$) and -2.75D defocus (F_{10} = 55.561, $p < 0.01$).

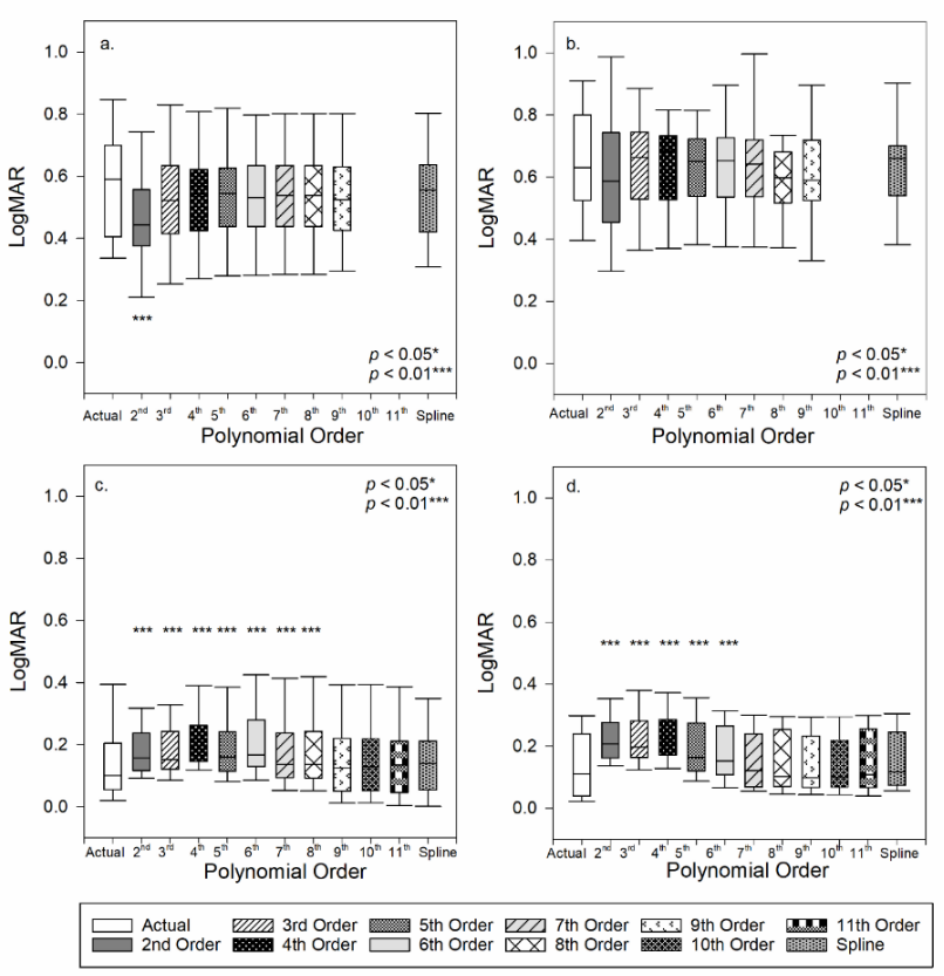


Figure 2.4: Comparison of means for additional defocus poi**nts.** Error bars = standard deviation

a. -2.25D defocus Bi-Flex 677AB
b. -2.75D defocus Bi-Flex 677AB
c. -2.25D defocus Bi-Flex MY
d. -2.75D defocus Bi-Flex MY

Post-*hoc* testing showed pairwise differences between the actual VA and those generated with 2^{nd} to 8^{th} order polynomials with defocus of -2.25 and 2^{nd} to 6^{th} order with defocus of -2.75D (**Figure 2.4c and 2.4d**). In the multifocal group, using a polynomial of insufficient order led to an under-estimation of the visual acuity.

In the monofocal group, a significant difference (**Figure 2.4a**) was found at -2.25 defocus (F_8=9.146, p <0.01). Post-*hoc* testing found a pairwise significant difference when using a 2^{nd} order polynomial only. With -2.75D of defocus, the differences were not significant (F_8 =1.947, p = 0.05) (**Figure 2.4b**).It was not possible to fit 10^{th} and 11^{th} order polynomials to the monofocal data, as the majority of participants had VA <1.00LogMAR at defocus -4.00 and above, hence insufficient data points were recorded to facilitate these higher order polynomials.

There was a strong correlation (R > 0.75) between the actual VA measured at -2.25 and -2.75D and the predicted values as calculated using each of the polynomials and cubic spline curve. In the monofocal group (Bi-Flex 677AB), maximum R^2_{adj} was found with 3rd order polynomials (**Figure 2.5 and 2.6**). In the multifocal group (Bi-Flex MY) maximum R^2_{adj} was found with a 9^{th} order but R>0.95 for 7^{th} order and above (**Figure 2.7 and 2.8**).

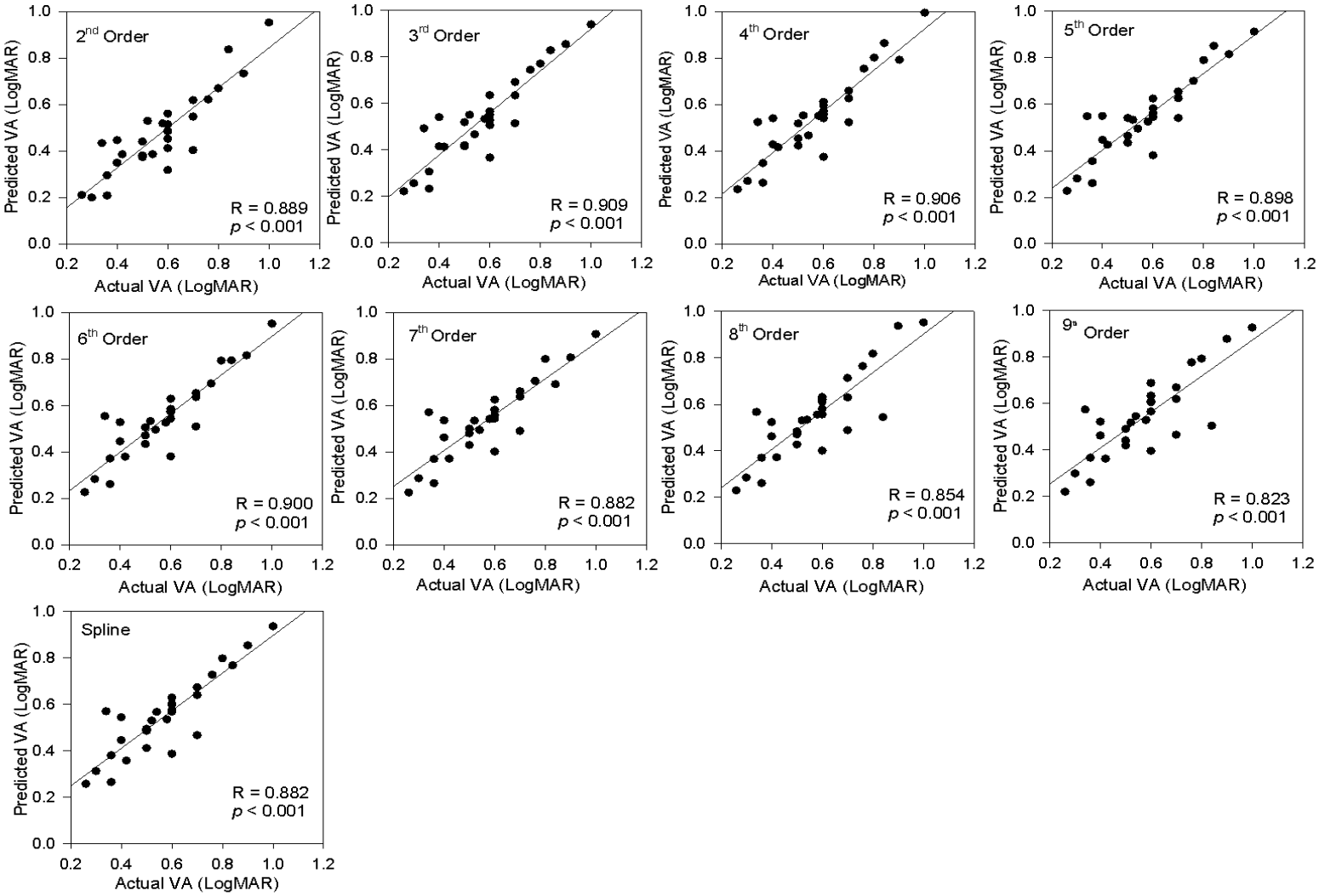


Figure 2.5: Correlation for Bi-Flex 677 AB with defocus of -2.25D

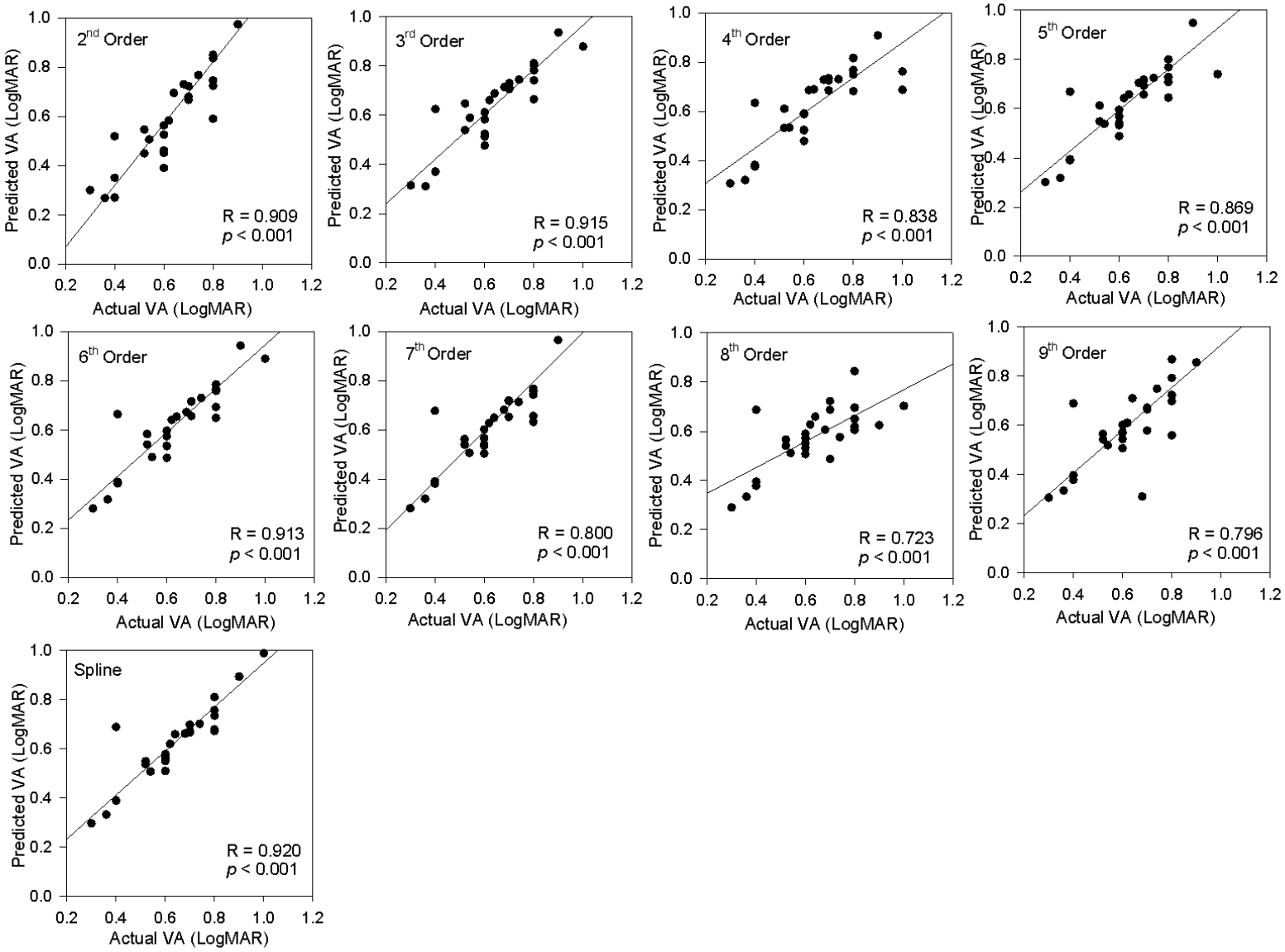


Figure 2.6: Correlation for Bi-Flex 677 AB with defocus of -2.75D

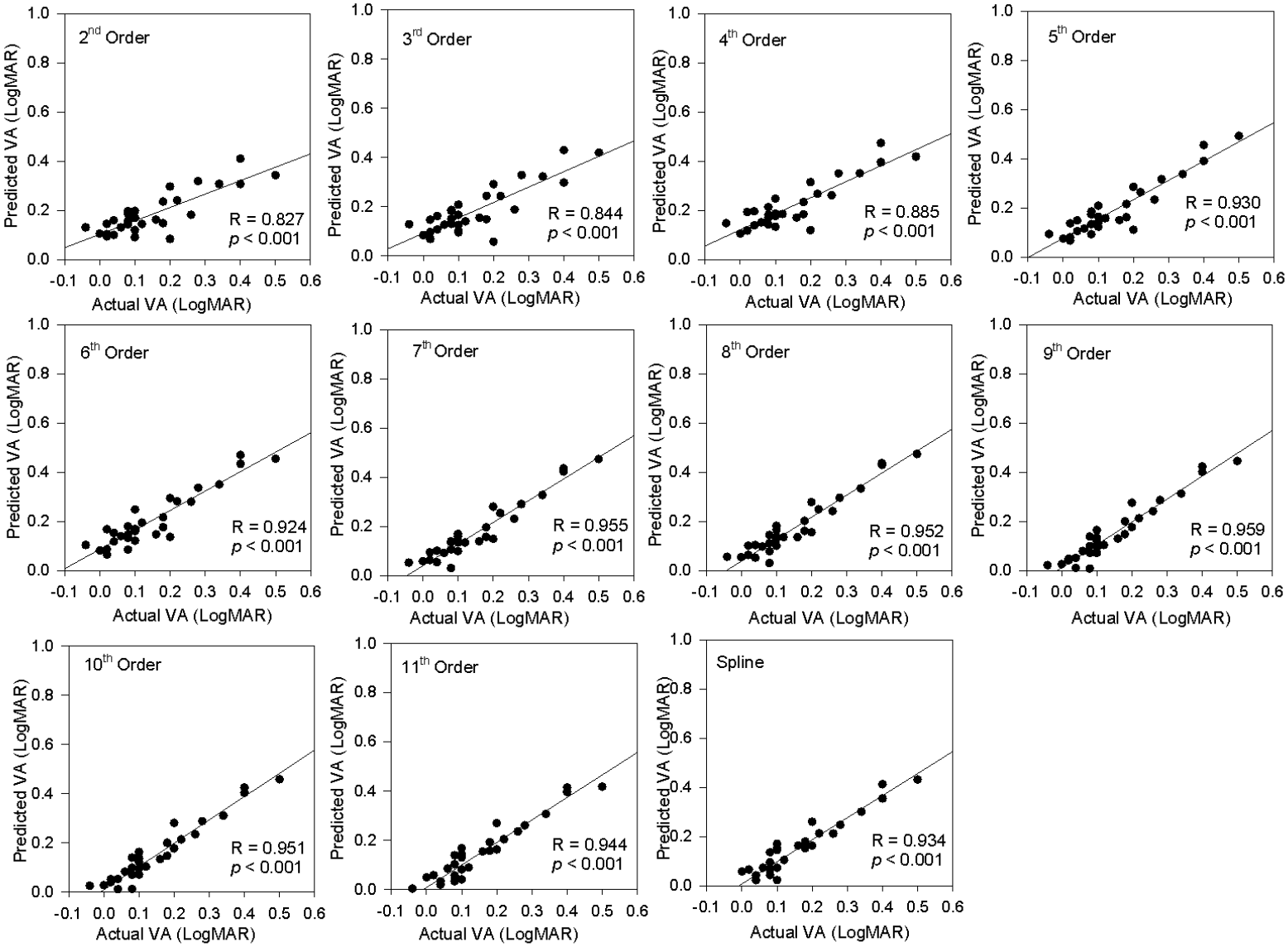


Figure 2.7: Correlation for Bi-Flex MY with defocus of -2.25D

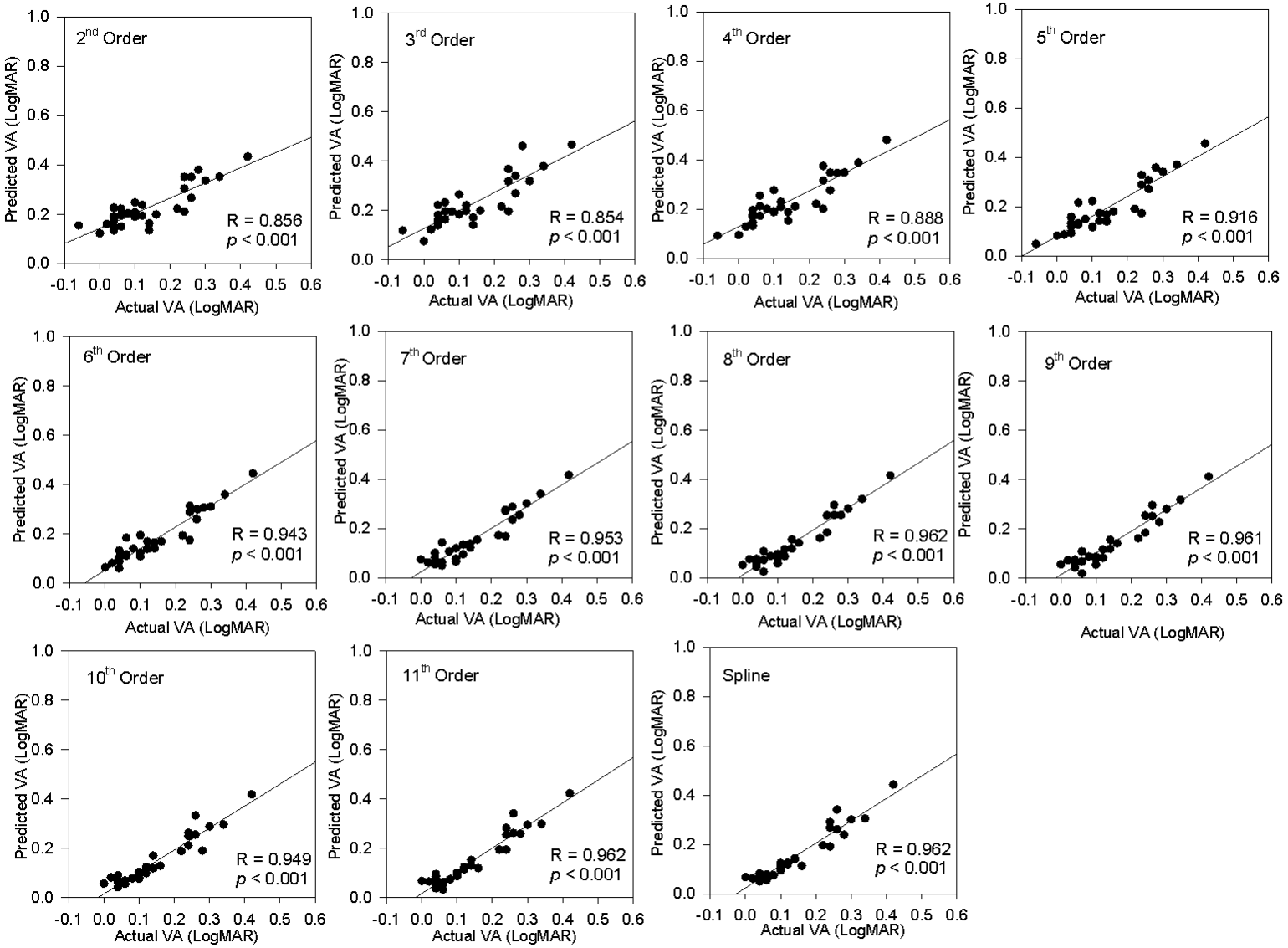


Figure 2.8: Correlation for Bi-Flex MY with defocus of -2.75

Difference vs mean plots taken from the monofocal IOL group demonstrated comparable means with the narrowest limits of agreement (LoA) occurring after the 3rd order polynomial for the 2.25D defocused acuity measurement and 5th order for the 2.75D defocused measurement (Figures 2.9 and 2.10).

However, for the MIOL group comparable means and narrowest LoAs were only achieved when using a 9rd order polynomial or higher for the -2.25D defocused acuity measurement and 8th order for the 2.75D defocused measurement (Figures 2.11 and 2.12).

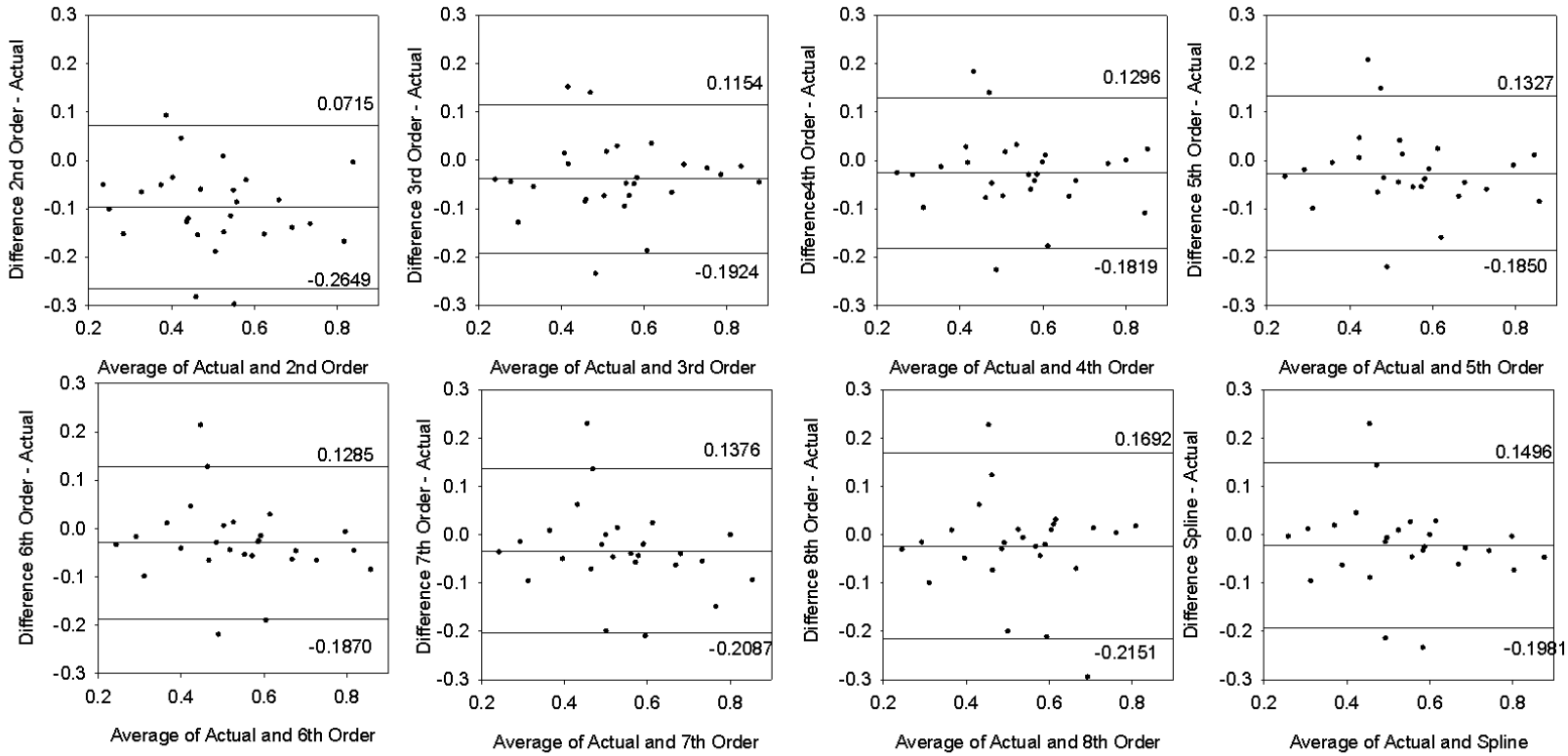


Figure 2.9: Bland Altman Comparison, Bi-Flex 677AB Monofocal of defocus -2.25D

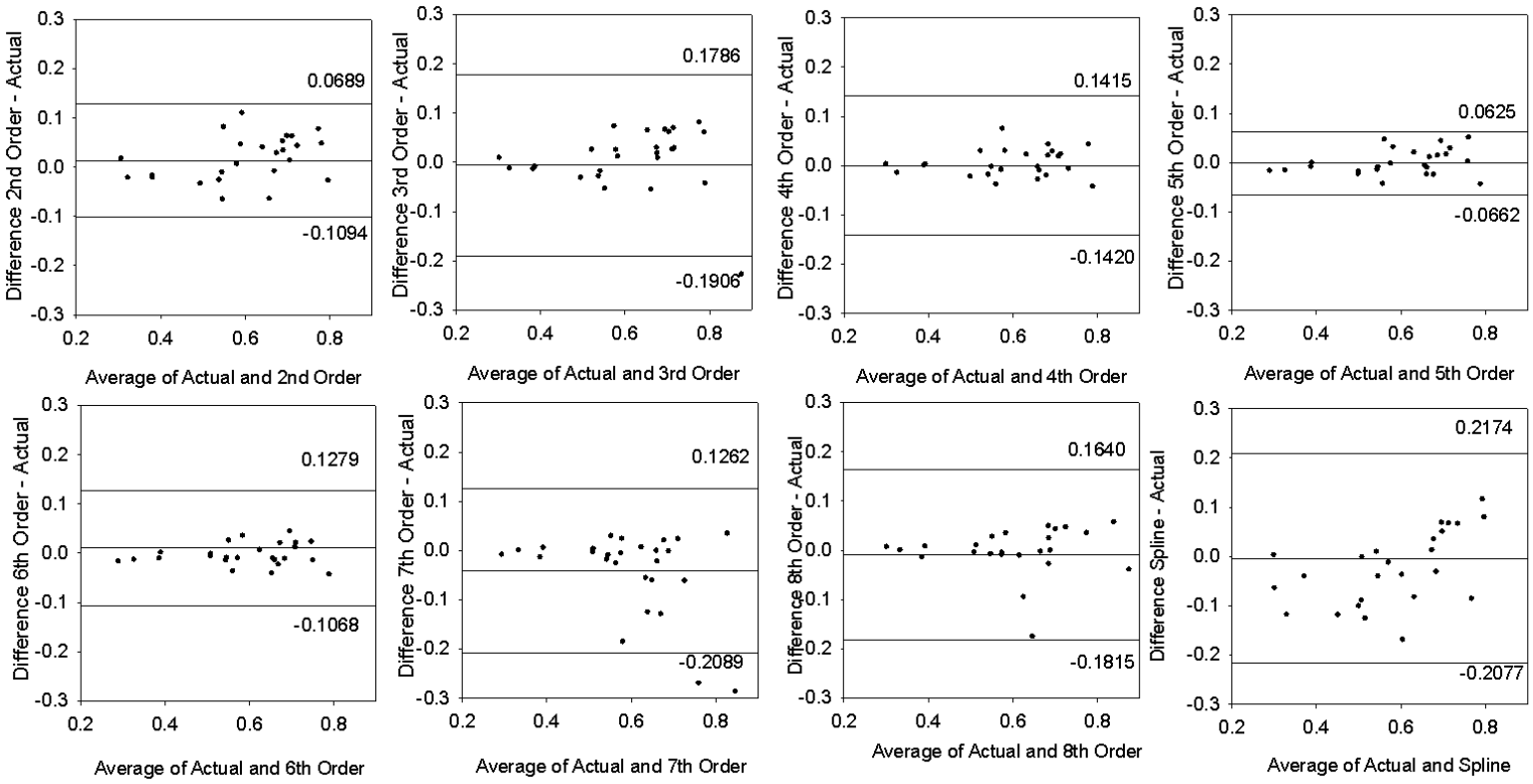


Figure 2.10: Bland Altman Comparison, Bi-Flex 677AB Monofocal of defocus -2.75D

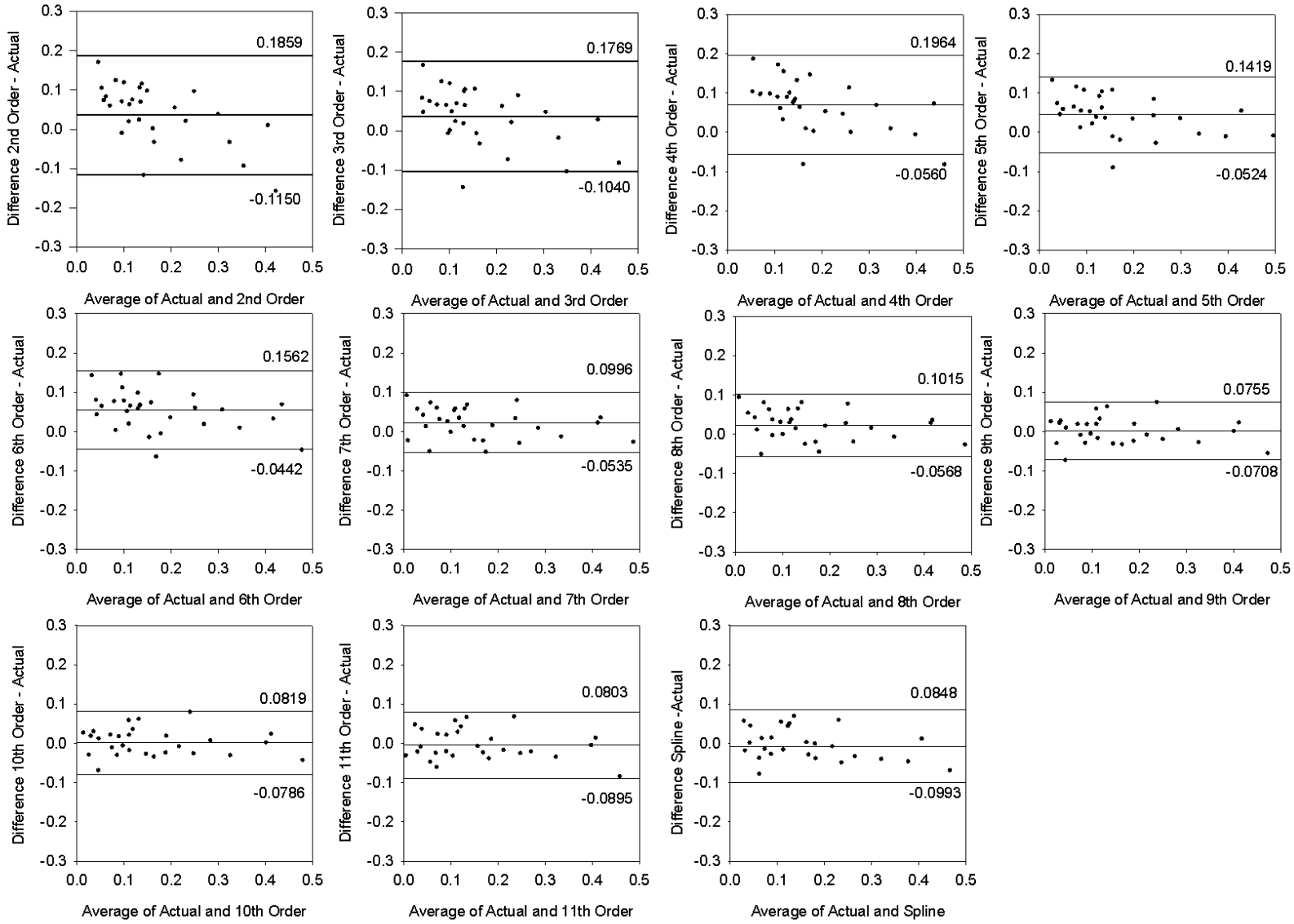


Figure 2.11: Bland Altman Comparison, Bi-Flex MY Multifocal of defocus -2.25D

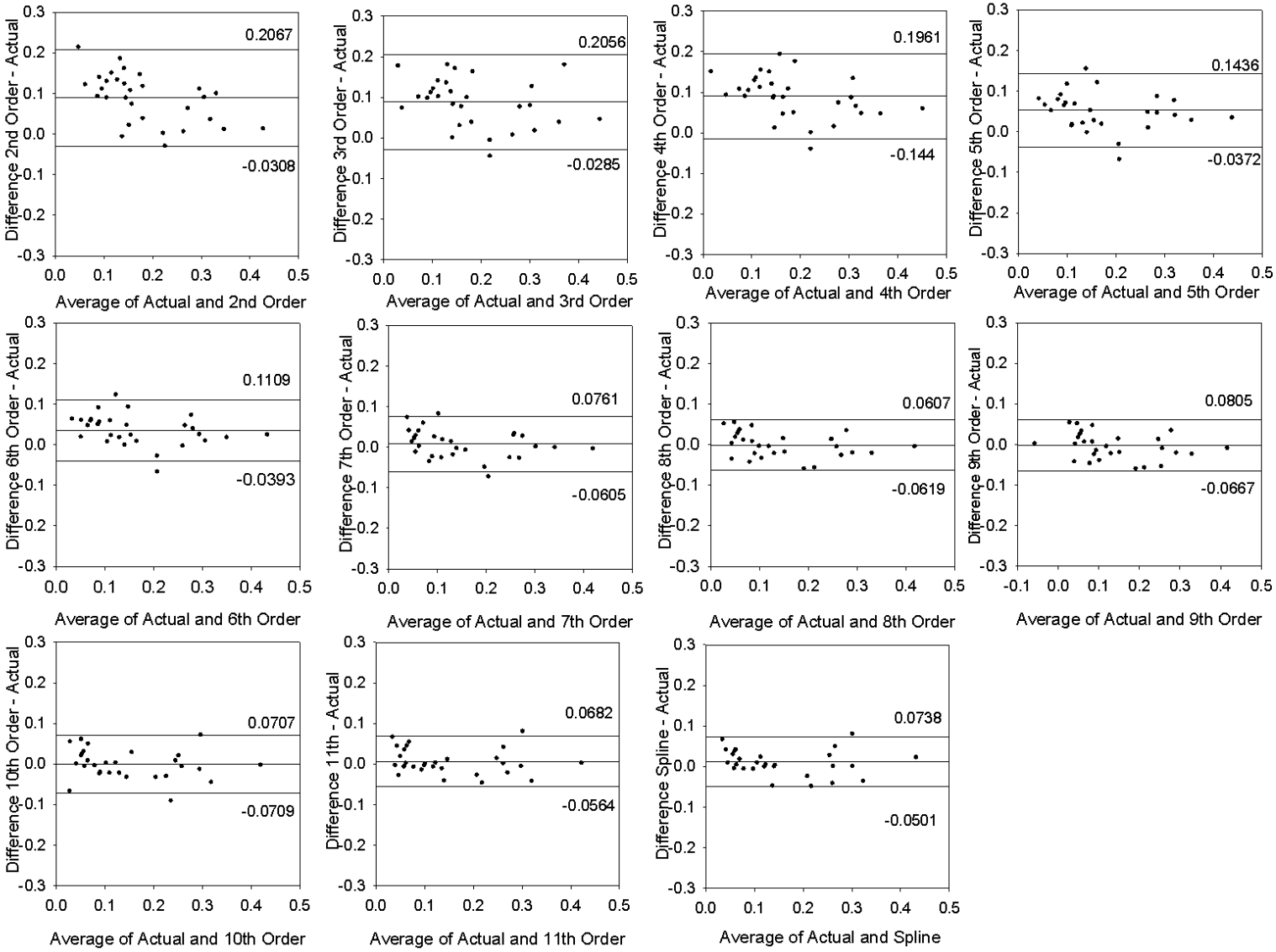


Figure 2.12: Bland Altman Comparison, Bi-Flex MY Multifocal of defocus -2.75D

Area of Focus was calculated for each lens according to the methods described previously (Buckhurst et al., 2012b). The areas derived from each of the polynomials were compared to those from the spline curve using repeated measures ANOVA and Bonferroni post-*hoc* pairwise comparisons revealed significant differences (**Figure 2.13**). Area distance (+0.50 to -0.50D defocus) required a minimum of a 7^{th} order polynomial for the Bi-Flex M and AT LISA trifocal and an 8^{th} order for the Bi-Flex 677AB and Mplus to provide similar results to the spline, yet the Symfony only required a 4^{th} order polynomial. Area intermediate (-0.50 to -2.00D defocus) again required higher order polynomials for the Bi-Flex M(7^{th}), AT LISA trifocal(7^{th}) and the Mplus (8^{th}), yet only lower order polynomials were required for the Bi-Flex 677AB (2^{nd}) and the Symfony (3^{rd}). For near area of focus (-2.00 to -4.00D), again low orders were required for the Bi-Flex 677AB (3^{rd}) and Symfony (3^{rd}). However, the Bi-Flex MY (6^{th}), Mplus (6^{th}) and AT LISA Trifocal (7^{th}) require higher order fitting.

The minimum polynomial order required for each metric to provide similar areas to the spline curve is outlined in **Table 2.5.**

Similar results were found when absolute range of focus was analysed using a cut-off value of 0.30 LogMAR (**Figure 2.14**), significant differences between range of focus derived from polynomials and spline curves were found statistically but no clear pattern established.

Table 2.5: Minimum polynomial similar to spline

	Area Distance	Area Intermediate	Area Near	RoF Total	RoF Actual
Bi-Flex 677AB	8^{th}	2^{nd}	3^{rd}	5^{th}	5^{th}
Bi-Flex MY	7^{th}	7^{th}	6^{th}	4^{th}	6^{th}
Mplus	8^{th}	8^{th}	6^{th}	2^{nd}	2^{nd}
Symfony	4^{th}	3^{rd}	3^{rd}	5^{th}	5^{th}
AT LISA 839	7^{th}	7^{th}	7^{th}	2^{nd}	2^{nd}

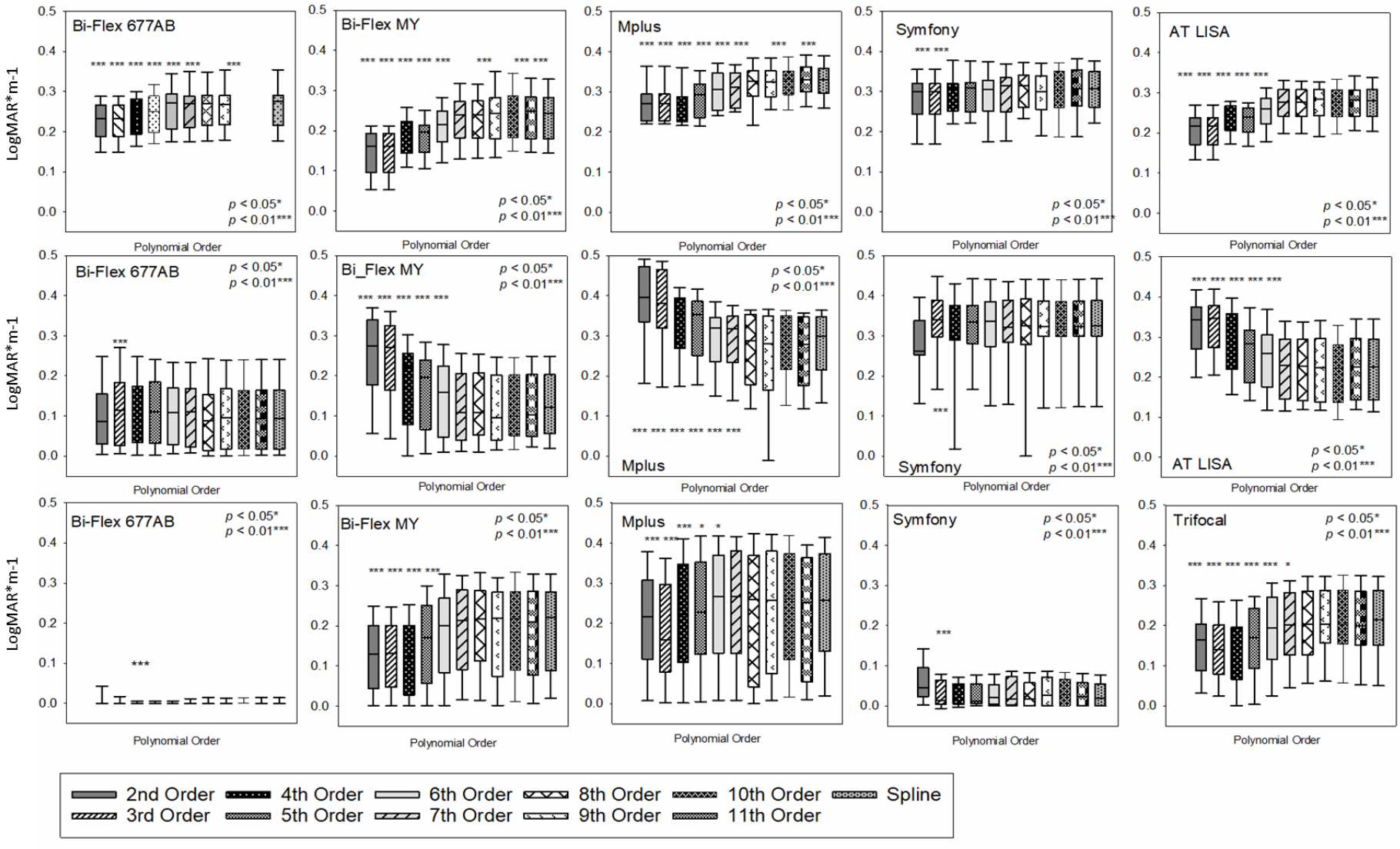


Figure 2.13: Area of Focus a. Distance b. Intermediate c. Near. Error bars = standard deviation

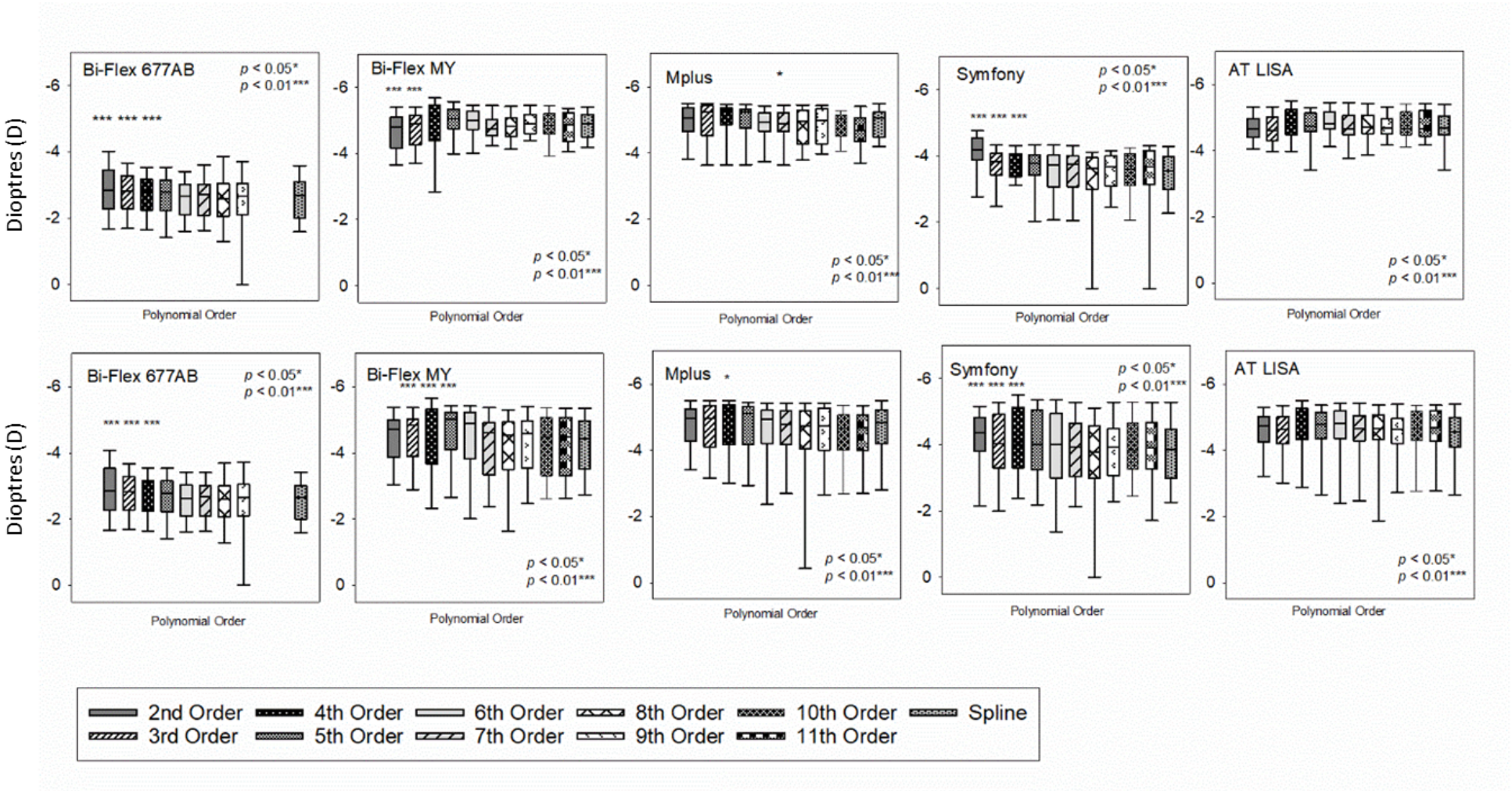


Figure 2.14: a. Range of Focus total b. Range of Focus actual. Error bars = standard deviation

2.9 Discussion

The study aimed to establish the method of choice for assessing goodness of fit when fitting curves to defocus data and to determine the polynomial most suited to defocus data, yet it demonstrates the inherent difficulties faced when selecting a single polynomial function that is the best fit to a combination of monofocal, bifocal, EDoF and trifocal IOLs. The statistical methods used to assess goodness of fit demonstrated variable results. This study found that the more lenient methods such as adjusted R^2 or the least squares methods can easily lead to overfitting , this is similar to the finding of Yang when assessing GoF (Yang L, 2008). As such, these methods are insufficient when used in isolation to select a polynomial for defocus analysis. To some extent, visually inspecting the fit can help prevent overfitting (Yang L, 2008) and will aid to exclude curves compromised by Rungé phenomena and other anomalies. Buckhurst (Buckhurst et al., 2012b) found a 9^{th} order polynomial was the universal best fit for his group, however this study indicates that this constitutes overfitting in the monofocal and EDoF groups. Gupta (Gupta et al., 2008) used a variety of 5^{th} to 10^{th} order polynomials in their work, based on achieving the highest possible R>0.99. It is known that deceptively high R values can be achieved when data is overfitted, thus measures such as adjusted R^2 are more commonly used to ensure that the increase in R is more than would be expected by chance (Anderson-Sprecher, 1994).

More stringent model fitting methods such as AICc and Snedecor & Cochrane are specifically designed to guard against over fitting and as such, show lower orders to be sufficient. Again, visual inspection will reveal when expected inflections in the defocus curve are omitted by the curve in favour of smoothing of the data and can guard against under fitting. These inflections points typically demarcate intermediate and near focus and as such are crucial for accurate

defocus analysis. Spline curves, which by nature will pass through each raw data point, will not omit these crucial peaks and troughs in the defocus profile.

A validation exercise was performed as part of this study, in order to assess the accuracy of VA extrapolated from the curve fitted compared to actual VA measured at additional data points of -2.25 and -2.75D defocus. Comparison of the means in this study found significant differences in both groups, amongst the monofocal group there was no significant difference when a 3^{th} order polynomial or higher was used. In the bifocal group, at least an 8^{th} order polynomial was required to achieve comparable results with the actual measured values of acuity. Using a polynomial of insufficient order in the monofocal group resulted in an overestimation of VA, whereas in the bifocal group using a polynomial of insufficient order resulted in an underestimation of VA (Figure 2.4). However, it must be considered that some variation between predicted *y* values and actual measured values will always exist, as actual measurements are limited to 0.02 LogMAR steps (1 letter). These results are also limited as they were not tested for the trifocal, refractive bifocal or EDoF lens.

Good correlation was achieved when validating the additional points measured in both groups with all curves fitted, however the correlation coefficient improves in the Bi-Flex 677AB monofocal group when either a spline curve or a lower order polynomial is fitted. Conversely in the bifocal group (Bi-Flex MY) higher order polynomials or spline curves improve correlation. This is also supported by our Bland-Altman analysis.

Assuming the spline curve data to be most accurate for assessing area of focus as it passes through each data point. Table 2.5 details the minimum polynomial required to reveal no significant differences in the area metrics when compared to the spline curve data. The order required varies depending on specific measure and thus there is no consistency even within an IOL group, nor was there any agreement between lenses.

2.10 Limitations

Although a validation exercise was carried out for two of the five IOLs, it would have been preferable to complete this exercise for all IOLs involved. It could also be beneficial to plot defocus curves in 0.25D steps rather than 0.50D to improve the resolution particularly around the expected inflection points however this would potentially exacerbate any inaccuracies from patient fatigue as it would increase the time taken to plot a defocus curve.

In addition, independent repetition of the visual inspection analysis by a second observer in would be desirable.

2.11 Conclusion

Defocus curves are widely used in the literature and with the advent of EDoF lenses and an increasing range of MIOLs, it is likely that defocus analysis will remain prominent as simple VA testing at arbitrary distances may be insufficient to differentiate between MIOLs or conversely it may bias results unfairly in the favour of a particular MIOL. To allow fair comparison of defocus metrics in IOLs, it is essential that their defocus curves can be analysed with a simple yet robust method. There is currently a paucity of literature using curve fitting in defocus metrics, most authors preferring to use direct analysis only, despite the benefits of range of focus and area metrics having been established (Buckhurst et al., 2012b, Gupta et al., 2008). It is possible that this may be due to the complexities inherent with polynomial curve fitting and the lack of agreed methodology previously published. The aim of this study was establish appropriate goodness of fit testing when curve fitting to defocus data and to establish the most appropriate fit. However, this study could not establish a conclusive method for choosing a

polynomial fit, nor could it establish a polynomial order that universally suited all the IOL types tested. The cubic spline curve appeared consistent throughout testing methods. By using piecewise polynomials, it guards against the issues of overfitting. Despite its benefits, the use of spline curves does require complex mathematical modelling to derive the desired metrics, thus it may not be accessible to all. Alternatively, should spline fitting not be readily available, our study would suggest the method of choice for choosing a polynomial order should be the adjusted R^2 method as some other goodness of fit strategies are simply too conservative in these circumstances. If the adjusted R^2 method is used, particular care and attention must be paid to curve fitting analysis to guard against both over and underfitting.

Thus, in summary the primary findings of this study are:

- For the analysis of the defocus profile of IOLs, the fitting of a spline curves is advocated
- With the exception of a spline curve, there is no agreement in polynomial order required to accurately fit differing IOL design
- Thus, goodness of fit must be assessed if fitting polynomials and the adjusted R^2 method is most appropriate

Detailed analysis of defocus profiles in MIOLs provides a valuable insight to the visual performance across a range of distances. It highlights the peaks of visual acuity in the distance and near range. The dioptric distance between these peaks should coincide with the addition power of the MIOL. Chapter 3 uses this curve fitting method to facilitate exploration of this addition power in MIOLs.

2.12 Supporting Publications

Chapter Two formed the basis for:

Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. Optimising curve fitting techniques to enable standardised analysis of defocus curves derived from multifocal intraocular lenses. *J Cataract Refract Surg*. Under Review

Chapter Three

An observational study exploring clinical methods for predicting post-operative addition power of a multifocal intraocular lens

OVERVIEW

Multifocal Intraocular lenses are commonly discussed in terms of their labelled addition power at the IOL plane. However, the addition power at the spectacle plane is the relevant metric. It is known that the addition power at the spectacle plane may differ in individuals depending on their anatomical features and effective lens position of the IOL.

This study assesses the post-operative addition power achieved at the spectacle plane with a bifocal IOL and aimed to identify a clinical method to predict this using IOL calculation formulae.

There was considerable variation in post-operative addition power achieved at the spectacle plane in our study group and we found the Barrett II Universal formula to offer the best predictive method.

3.1 Introduction

Similar to multifocal spectacles, multifocal IOLS (MIOLS) can provide correction for distance, near and/or intermediate vision. Unlike corrections provided by spectacles, there is a limited range of near corrections available, choosing the most appropriate correction is complicated further by the description of the power of the lens, as it is provided at the IOL plane. Despite the fact that addition power at the spectacle plane provides a better reflection of the actual near working distance provided by a multifocal intraocular lens (MIOL) and thus is the clinically valuable metric, manufacturers do not offer this information and instead only describe near addition power at the IOL plane. In phakic presbyopes, the choice of spectacle addition power is dependent on many factors including the patients age, their physical characteristics, distance refractive error and preferred working distance as required for their lifestyle (du Toit, 2006). Depending on a patients working life or hobbies, differing near working distances could be advantageous, similarly a patient with longer arms, may be physically more comfortable with a longer near working distance. Optometrists consider all of these factors routinely when prescribing multifocal spectacles and these principles could be applied to surgery to allow a personalised medicine approach, and thus potentially improve patient outcomes. The literature does encourage surgeons to undertake a similar approach with extensive pre-operative counselling of patients with particular attention to the patient's lifestyle and expectations when considering surgical presbyopic correction (Braga-Mele et al., 2014, Davidson et al., 2016, Pepose, 2008, Sachdev and Sachdev, 2017). The ability to predict to post-operative addition power would further enhance this approach. MIOLs are available in diffractive or refractive designs, as discussed in Chapter 1. Near addition powers ranging from +1.50D to +4.00D at the IOL plane are available, thus there is the potential to tailor near addition power to a patient's needs.

3.1.1 Effective Addition Power

Previous literature demonstrates that the optimal near focal point achieved with an MIOL varies in individuals despite a fixed labelled addition power (Eom et al., 2017, Petermeier et al., 2009b, Savini et al., 2016). Effective addition power (addition power achieved post-operatively) is dependent on both the power of the base IOL and an individual's ocular biometry, thus being able to predict the post-operative effective addition is crucial (Holladay and Hoffer, 1992, Savini et al., 2016). Holladay demonstrated that in order to achieve 3.00D in the spectacle plane, MIOL addition power required at the IOL plane could vary from 3.3D to 5.1D (Holladay and Hoffer, 1992). Similarly, Hoffer reported that the manufactured addition power of an MIOL required to achieve 2.75D in the spectacle plane was greater in individuals with deeper anterior chambers and noted that increasing axial length (AL) or increasing corneal power (K) resulted in a lower addition power achieved (Hoffer, 1991, Holladay and Hoffer, 1992).

3.1.2 Effective Lens Position

Effective lens position (ELP) is the term used to define predicted post-operative position of the IOL in the eye. Actual lens position (ALP) can only be measured post-operatively, thus, clinicians must rely on predicted ELP. ELP was found to exert the greatest effect on the achieved addition power (Holladay and Hoffer, 1992). This was further supported in a theoretical study, which used model eyes to illustrate that longer eyes with steeper corneas thus an increased effective lens position (ELP)(greater distance between cornea and expected lens position), had the furthest near focal point (lower dioptric addition power) (Savini et al., 2016). It has been shown that a major source of error in IOL power calculations is inaccuracy in the predication of ELP (Norrby, 2008).

3.1.3 Prediction of addition power

Eom (Eom et al., 2017) compared an MIOL manufacturers' prediction of spectacle plane addition power to addition power determined from defocus curves and calculations of ELP, and again concurred that increasing ELP resulted in lower MIOL addition power at the spectacle plane . They also surmised that pre-operative calculation of ELP was a better indicator of resultant add power than the manufacturers' predictions. Petermeier (Petermeier et al., 2009b) established differences in effective addition power in myopes and hyperopes and found a correlation between axial length, anterior chamber depth and post-operative reading distance. Modern biometry formulae have been shown to be accurate predictors of the spherical component of the distance refractive error post-operatively (Olsen, 2007). Application of these formulae to addition powers could allow estimation of near spherical equivalent and would better allow clinicians to tailor MIOL choice to a patient's individual needs and maximize visual performance for near vision, yet to date this has not been explored in the literature

This prospective study was designed to explore the relationship between both the theoretical addition power and the effective addition power at the spectacle plane using actual post-operative data.

The primary aims of this study were to

- Assess post-operative effective addition power with a MIOL
- Compare effective addition power to theoretical addition power
- Explore a simple clinical technique for predicting the post-operative add power using IOL formulae

3.2 Study Design

This was a prospective study, part of a larger RCT (Chapter 4). Ethical approval was obtained from South West Ethical committee on 9th March 2015, (Ref:15/SW/0027, IRAS 165928) and adheres to the tenets of the Declaration of Helsinki (Appendix 1). All subjects gave written informed consent. In total, 50 subjects were recruited who were bilaterally implanted with a diffractive MIOL with an addition power of +3.50D at the IOL plane. Post-operatively, 1 subject was excluded due to a surgical complication, and 3 failed to attend follow up visits. 46 subjects attended the study visit, but 5 were excluded as their post-operative biometry had insufficient information (n=3), or IOL calculations (Hill RBF) considered the data out of bounds (n=2).

3.2.1 Patient Selection

Subjects who met the inclusion/exclusion criteria (Table 3.1) were recruited from routine cataract clinics at the BMI Southend hospital.

Table 3.1: Inclusion/Exclusion Criteria

Inclusion	Exclusion
Age related cataract requiring bilateral cataract surgery with phacoemulsification	Subjects with retinal pathology
Participants requiring primary IOL implantation	Previous intraocular and/or corneal surgery
Participants with a potential corrected visual acuity of 0.3 LogMAR or better on clinical assessment in both eyes	Subjects using a systemic medication that is known to cause ocular side effects
Subjects with clear intraocular media and normal anterior segment other than cataract	Subjects participating in a concurrent clinical trial or if they have participated in an ophthalmology clinical trial within the last 30 days
Participants aged 18+ years	Pregnant women
< 1.00D of preoperative corneal astigmatism	Subjects who could not make an informed consent

3.2.2 Masking

As this study was part of a larger RCT (Chapter 4) and as such subjects were not aware of the addition power of the IOL nor the expected reading distance. The same clinician performed all post-operative study assessments and was also masked to the IOL implanted.

3.2.3 Intraocular Lenses

All subjects were bilaterally implanted with the Bi-Flex MY MIOL with +3.50D addition power (Table 3.2).

Table 3.2: IOL Characteristics

	Bi-Flex MY
Material	Copolymer of hydrophilic and hydrophobic acrylic
Blue Filter	390-470nm
Aspheric	Yes
Design	Diffractive Bifocal +3.50 Add
Refractive Index	1.46
Abbe	58
Range	0 to 30D (0.50D steps) 31 to 35D (1.00D steps)
Optic Diameter	6mm biconvex
Overall Length	13mm
Haptic	0.4 thickness with 0° angulation

3.3 Surgery

All surgeries were performed by one of two experienced consultant ophthalmic surgeons (RA (n = 28) and HK (n=13)) using topical anaesthetic and small incision phacoemulsification. The same surgeon implanted both lenses for an individual subject.

3.3.1 Pre-Surgery Medication

Anaesthesia was achieved by topical administration of Minims®Proxymetacaine hydrochloride 0.5% (Bausch & Lomb) eye drops prior to and during surgery. Pupil dilation was achieved by topical application of the mydriatic agents, Minims®Tropicamide 1% (Bausch & Lomb) and Minims®Phenylephrine 2.5% (Bausch & Lomb) and oral administration of 250mg Acetazolamide was also implemented as routine practice.

3.3.2 Surgical Technique

Surgery was performed by small incision phacoemulsification as detailed in Section 1.5.4, the OVD used was Hydroxypropyl Methylcellulose (HPMC) and both surgeons used a clear corneal incision of 2.2mm located according to the steepest corneal meridian. Finally, 1% cefuroxime was instilled intracamerally.

3.3.3 Post-Surgical Medication and Advice

Following surgery, the subjects were instructed to use Tobradex 3mg/ml/1mg/ml (Novartis) four times daily for four weeks following surgery. Standard post-operative advice was provided verbally and as an information leaflet.

3.3.4 Post-Operative Visit

Following surgery to their first eye, the subject was requested to attend a routine post-operative check one week after surgery. If no complications were identified then the subject was given a surgical date for the second eye within 3 weeks.

3.4 Method

The same investigator assessed the subjects at 3-6 months post-operatively. The same assessment room was used throughout the study and all tests were carried out in photopic light conditions of illuminance 120cd/m^2 and luminance of 95 lux.

Visual Acuity was measured at both distance (6m) using the electronic Thomson Chart (Thomson Software Solution, Herts, UK) and at near (40cm) (LogMAR Chart 2000, Precision Vision TM, La Salle, IL, USA). Subjective manifest refraction was performed to establish best distance correction with a back vertex distance (BVD) of 12mm. Defocus profiles were plotted with manifest refraction worn. Pre and post-operative biometry measurements were taken using the LenSTAR (Haag-Streit AG, Koeniz, Switzerland). Effective Addition Power, Theoretical Addition Power and Predicted Addition Power were calculated using the methods below.

3.4.1 Effective Addition Power

Monocular defocus curves from +1.50D to -5.00D in 0.50D randomised steps were measured as described in Section 2.6.1 and adhering to previously published methodology (Gupta et al., 2007, Gupta et al., 2008, Wolffsohn et al., 2013). In order to establish the effective addition achieved by individual subjects, the dioptric distance between the maximal acuity in the

distance range of the defocus curve and the maximum acuity in the near defocus range was calculated and we referred to this forthwith as Simple effective addition power. By using 0.50D steps, this meant simple effective addition power could only be resolved to 0.50D. To further improve the resolution, a cubic spline curve was fitted to the defocus curve data as per the method described in Chapter 2 and the distance and near focal points were identified by deriving the inflection points of the curves using MATLAB R2017b (The Mathworks Inc, Natick, MA, USA). The effective addition power achieved by a subject was defined as the dioptric distance between the distance and near inflection points (Figure 3.1).

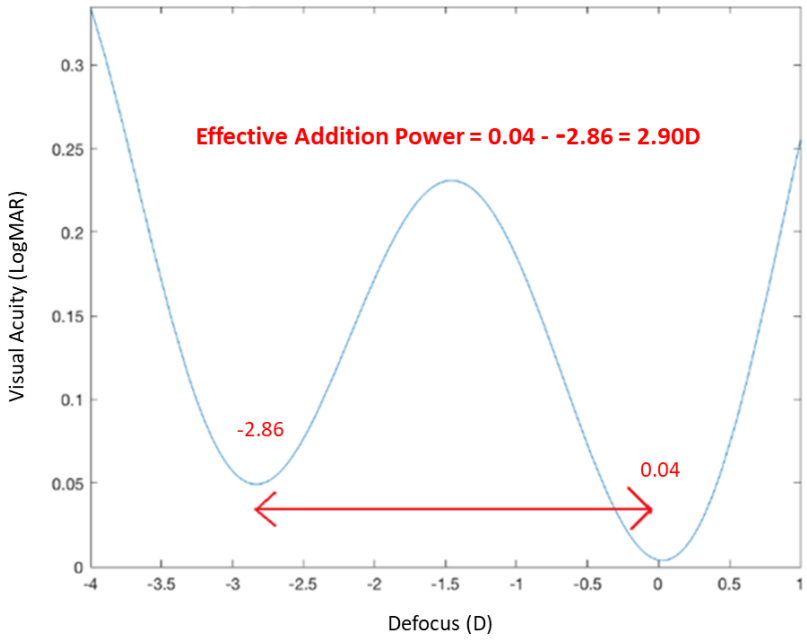


Figure 3.1: Example of effective addition power from an individual subject derived from cubic spline fitting of defocus data

3.4.2 Theoretical Addition Power

The post-operative ocular biometry, actual lens position and known IOL power were used to calculate the theoretical add power by thin lens ray tracing calculations. This calculation was based on a simple eye model (Figure 3.2) according to paraxial ray tracing, assuming a

refractive index internally (aqueous humour and vitreous), n = 1.336 and a back vertex distance (BVD) of 12mm.

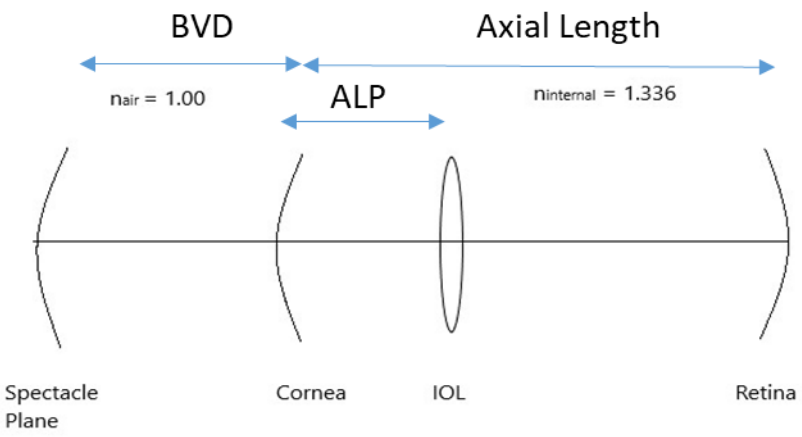


Figure 3.2: Simple Eye Model

Actual lens position (ALP) was calculated (**Equation 3.1**) using post-operative biometry data for anterior chamber depth (ACD) and lens thickness (LT).

$$ALP = ACD + \frac{LT}{2}$$

Equation 3.1: Actual Lens Position

Vergence was calculated at each surface, L (posterior IOL surface), L' (anterior IOL surface), L_2 (posterior corneal surface), L_2'(anterior corneal surface) and L_3 (spectacle pane) using equations 3.2 to 3.6 (**Figure 3.3**) (Bennett, 1998).

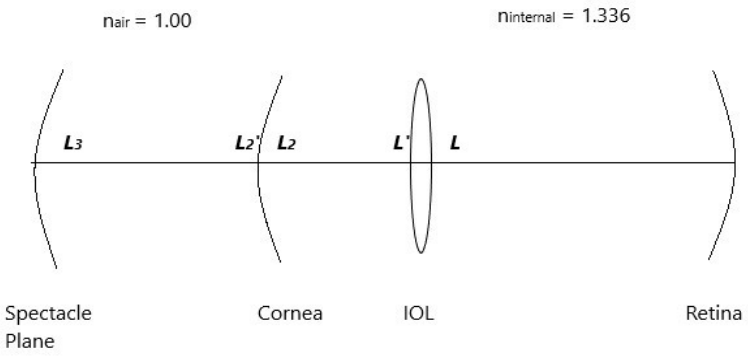


Figure 3.3: Vergence diagram

$$L = \frac{n_{internal}}{AL - ALP}$$

Equation 3.2: Vergence of light reaching posterior IOL surface

$$L' = L - IOL\ power$$

Equation 3.3: Vergence of light leaving anterior IOL surface

$$L_2 = \frac{n_{internal}}{ALP + \frac{n_{internal}}{L_1}}$$

Equation 3.4: Vergence of light reaching posterior corneal surface

$$L_2' = L_2 - K_{average}$$

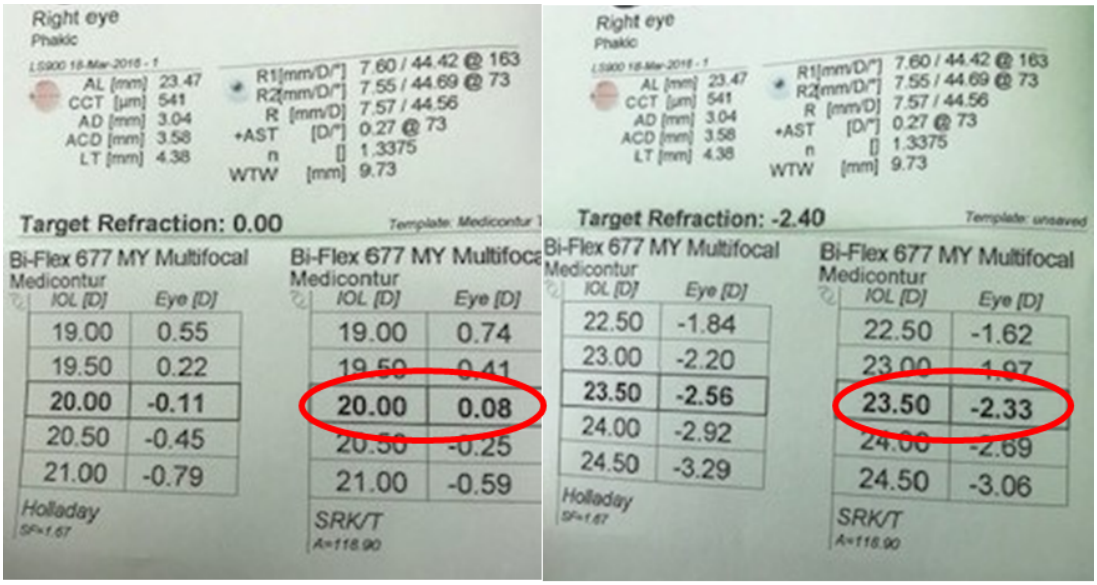
Equation 3.5: Vergence of light leaving anterior corneal surface

$$L_3 = \frac{n_{air}}{BVD + \frac{n_{air}}{L_2'}}$$

Equation 3.6: Vergence of light reaching spectacle plane

3.4.3 Predicted Addition Power

Pre-operative biometry results were used to predict the addition power according to the Haigis, Holladay, SRK/T, Hill RBF 2.0 and Barrett II Universal formulae by simply increasing the base IOL power by 3.5D and noting the predicted spherical equivalent. The difference between this value and the distance predicted spherical equivalent of the implanted IOL power was taken as the predicted addition power at the spectacle plane (**Figure 3.4**).



Predicted Add = 0.08 - -2.33 = 2.41D

Figure 3.4: Example of biometry prediction

3.5 Statistical Analysis

Statistical analysis was performed using SPSS software, version 24 (SPSS Inc, IBM, Armonk, NY, USA). All data were tested for normality using the Shapiro Wilks test and parametric testing or non-parametric testing used thereafter. In all instances, a *p* value < 0.05 was considered statistically significantly.

3.5.1 Sample Size

The a priori sample size for the study was calculated using G*power3 (Heinrich Heine, University of Dusseldorf, Germany) (Faul et al., 2007) and effect size assumptions from Cohen's tables (Cohen, 1988). For Pearson's correlation with a large effect size (r = 0.5), and a desired power of 80% with an error probability of 0.05 a minimum of 28 subjects were required. All 50 subjects from the RCT (Chapter 4) were included to allow for dropouts.

3.5.2 Similarity between eyes

A two-way repeated measures ANOVA was performed to establish similarity between right and left eyes, no significant differences were found. Correlation is expected to be high between eyes of an individual subject, thus including both eyes and ignoring the inter eye correlation can lead to quantitative errors in statistics (Ray and O'Day, 1985, Snedecor, 1967). Thus only right eye data is used thereafter.

3.5.3 Spectacle Magnification

All defocus data was corrected for spectacle magnification (SM) assuming a thin lens calculation with back vertex distance (BVD) of 12mm (Equation 2.2).

3.5.4 Validity of defocus data

Pearson's correlation coefficient was used to check the validity of the defocus data against distance and near acuity testing.

3.5.5 Analysis of prediction methods

The correlation between the effective, theoretical and prediction methods was assessed using Pearson's correlation. Bland-Altman analysis was also performed, and one-sample *t* tests was used to compare the differences between methods to zero.

In addition, analysis of the means was performed by repeated measures ANOVA comparing the effective, theoretical and predicted distance spherical equivalent and near spherical equivalent. Where differences were found, further *post hoc* analysis was used to highlight these differences.

3.6 Results

Forty-one subjects were analysed, 9 males and 32 females with a mean age of 76.76 ± 6.13. (**Table 3.3**). All subjects had excellent best-corrected distance visual acuity (CDVA) post-operatively (0.07±0.08 LogMAR) with minimal refractive error (post-operative spherical equivalent (0.00 ± 0.40D).

Table 3.3: Subject Demographics

Age	76.76 ± 6.13
Sex	9 Male (22%) 32 Female (78%)
Pre-Op Spherical Equivalent (D)	-0.30 ±2.21
***Pre –Op Refractive Error** **Myope** **Hyperope** **Emmetrope**	 15 (36.6%) 13 (31.7%) 13 (31.7%)
Pre-Op Axial Length (mm)	23.36 ± 1.06 Range 21.33 to 25.84
Pre-Op Anterior Chamber Depth (mm)	4.73 ± 0.37
Pre Op K (D)	43.39 ± 1.63 Range 40.19 to 47.41
Post-Op Spherical Equivalent (D)	0.00 ± 0.40
Post-Op CDVA (LogMAR)	0.07 ±0.08
IOL Power (D) **Range**	20.83 ±3.25 13 to 30
Mean ± Standard Deviation *Myopes defined as ≥-0.50D Hyperopes defined as ≥0.50D Emmetropes defined as <±0.50D	

There were no significant differences when pre- and post-operative measures of corneal curvature K1 (p = 0.74), K2 (p = 0.84) and axial length (p = 0.70) were compared. (**Figure 3.5**).

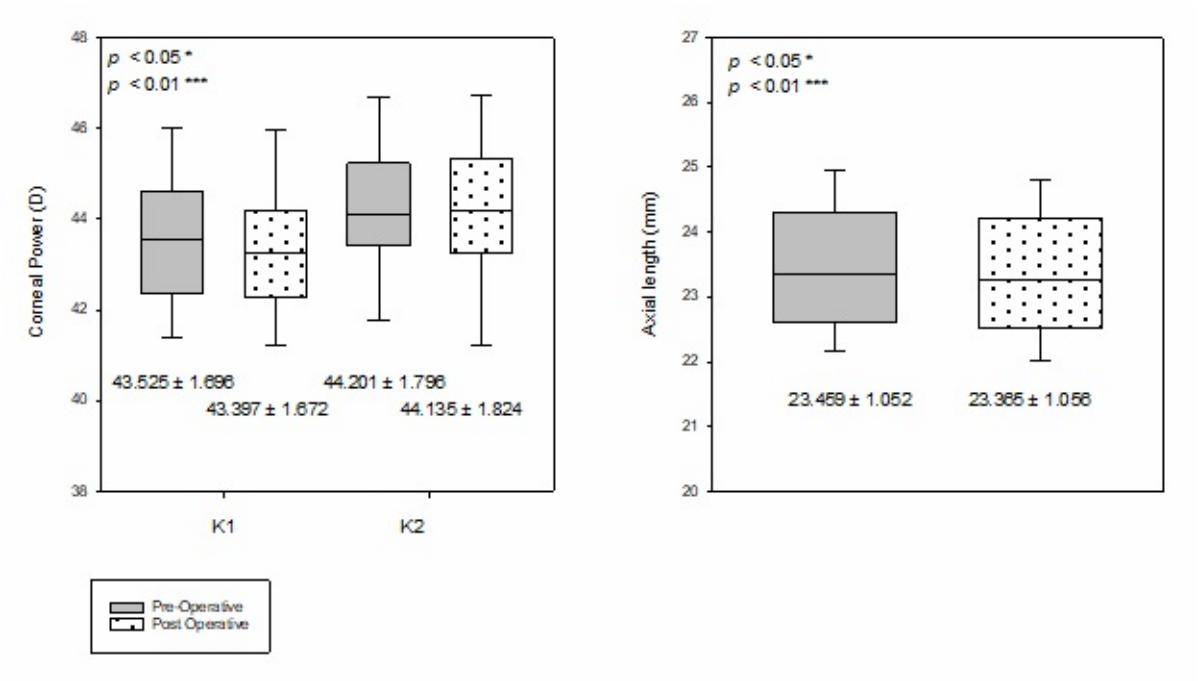


Figure 3.5: Comparison of Pre- and Post-Operative Biometry data. Error bars = standard deviation

To determine the validity of the defocus data, the defocus of -2.50 and 0 were checked against VA measures. There was a significant strong positive correlation between best-corrected distance acuity (CDVA) and zero defocus (R = 0.82, $p < 0.01$) and best distance corrected near acuity (DCNVA) at 40cm and -2.50 defocus values (R = 0.83, $p < 0.01$).

No significant differences between the methods for predicting distance spherical equivalent, and the actual measured data were found ($F_8 = 0.72$, $p = 0.65$). The mean effective addition derived from spline curve fitting to the defocus data was 2.60 ± 0.29, and ranged from 1.96D to 3.10D (Table 3.4; Figure 3.6).

No significant difference in the means ($p = 0.46$) was observed between the effective addition power derived from simple defocus data and that derived from fitting a spline curve to the data, thus the spline data only will be used when discussing effective addition power from this point onwards as the simple data is limited by resolution.

Table 3.4: Comparison of Methods						
	Refraction	Simple Defocus	Spline Defocus	Ray Tracing	Formulae	Prediction
Distance Spherical Equivalent (D)	0.00 ± 0.40	0.00 ± 0 .00	0.01 ± 0.18	0.20 ± 0.85	Haigis Holladay SRK/T Hill RBF Barrett	-0.08 ± 0.21 -0.09 ± 0.22 0.02 ± 0.15 0.07 ± 0.14 0.04 ± 0.18
Near Spherical Equivalent (D)	N/A	-2.55 ± 0.51	-2.59 ± 0.31	-2.73 ± 0.94	Haigis Holladay SRK/T Hill RBF Barrett	-2.68±0.21 -2.57±0.17 -2.46±0.31 -2.40±0.18 -2.52±0.24
Add (D)	N/A	2.55 ± 0.51	2.60 ± 0.29	2.54 ± 0.13	Haigis Holladay SRK/T Hill RBF Barrett	2.60±0.05 2.49±0.11 2.49±0.16 2.47±0.08 2.57±0.13
Mean ± Standard Deviation Add = difference between distance and near spherical equivalent						

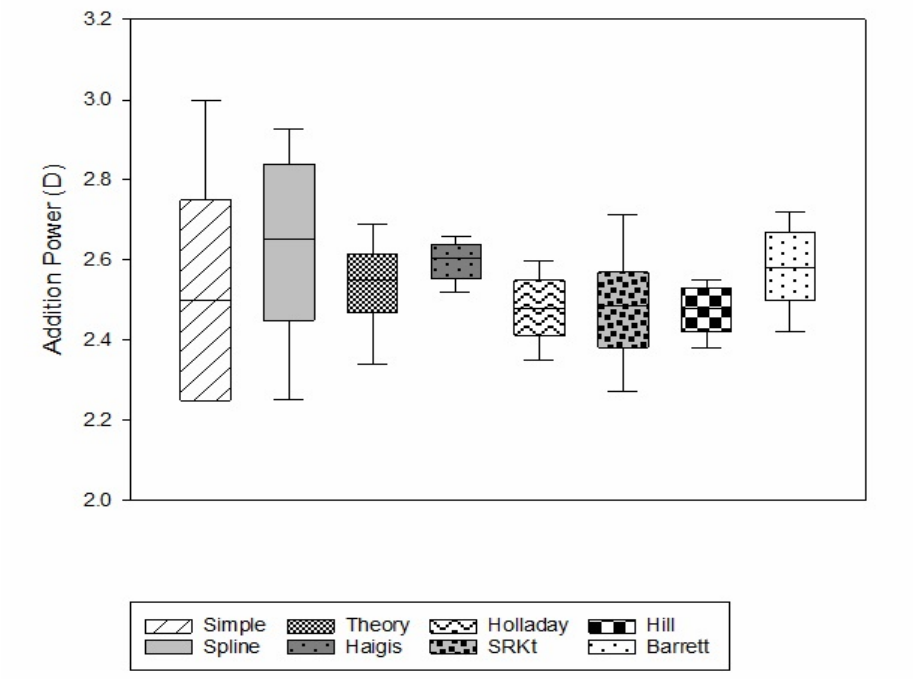


Figure 3.6: Comparison of Addition powers. Error bars = standard deviation

Similarity was found between the theoretical calculated addition power and the effective addition power (p = 0.22) but correlation was low (r = 0.17, p = 0.31).

However, there were significant differences between the methods for calculating and predicting near addition power ($F_7 = 4.39$, $p < 0.01$). *Post-hoc* analysis and Bonferroni correction demonstrated significant pairwise differences between the effective and predicted addition powers derived using the Holladay ($p = 0.01$), SRK/T ($p = 0.03$) and Hill RBF ($p < 0.01$) formulae. Whilst predicted values from the Haigis ($p = 0.91$) and Barrett II Universal ($p = 0.55$) formulae were similar to that of the effective addition power.

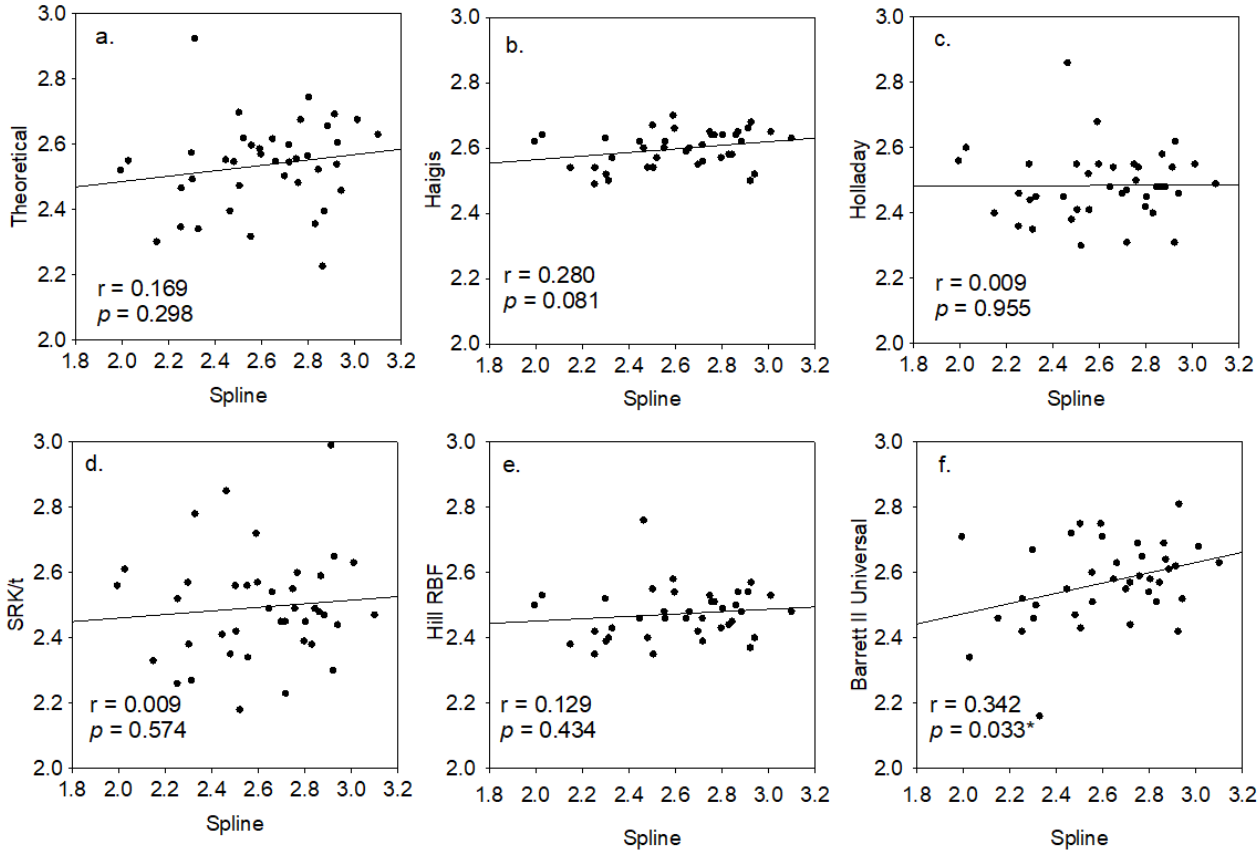


Figure 3.7: Correlation plots

a. Spline vs Theoretical
b. Spline vs Haigis
c. Spline vs Holladay
d. Spline vs SRK/T
e. Spline vs Hill RBF
f. Spline vs Barrett

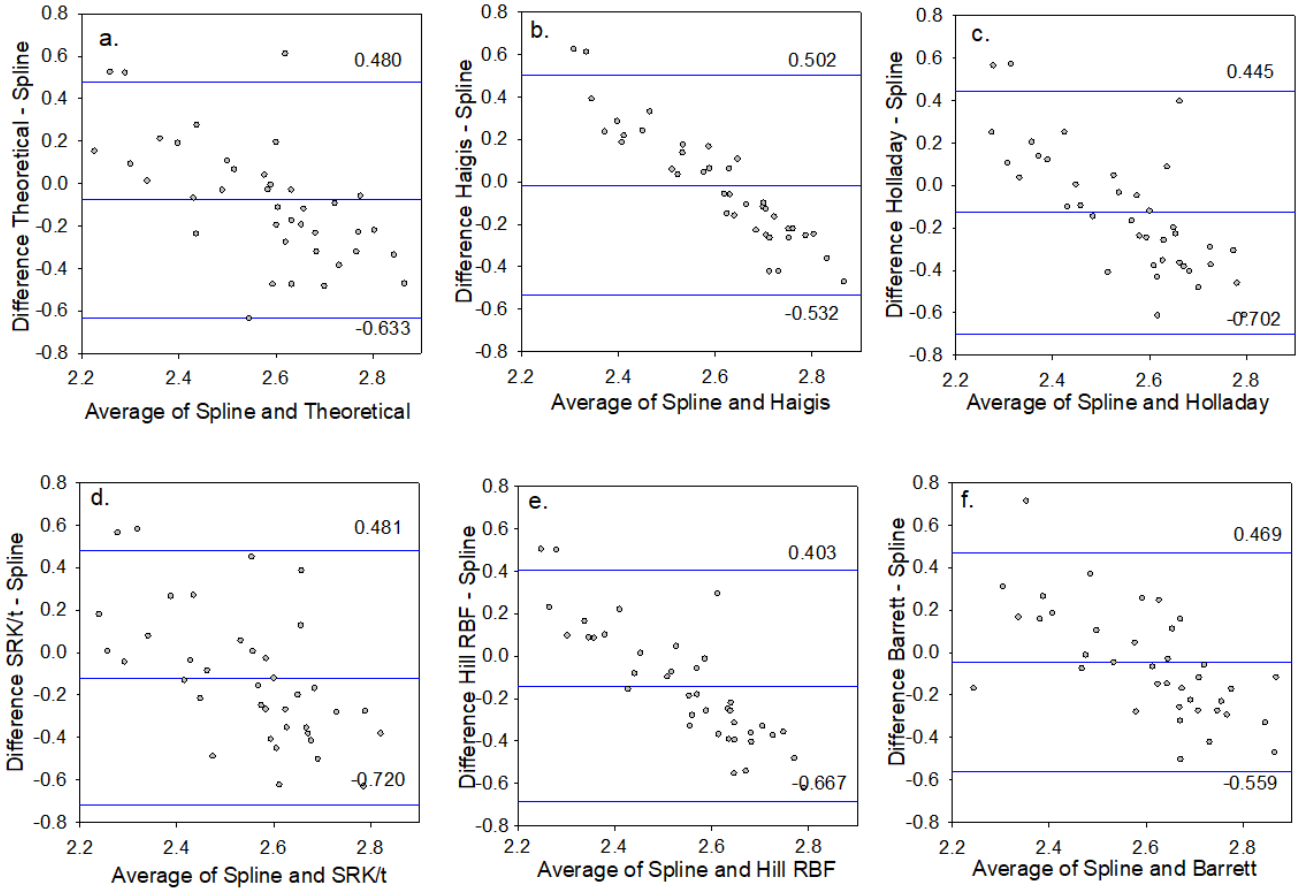


Figure 3.8: Bland Altman comparison of methods

a. Spline vs Theoretical
b. Spline vs Haigis
c. Spline vs Holladay
d. Spline vs SRK/T
e. Spline vs Hill RBF
f. Spline vs Barrett

There was also a significant positive moderate correlation between the effective and the predicted addition power derived from the Barrett formulae (R = 0.34, *p* = 0.03) (**Figure 3.7**). Bland Altman plots (**Figure 3.8**) showed that the mean difference was close to zero when effective addition power was compared to predicted values derived from the Haigis (-0.02) and Barrett (-0.04) formulae and the theoretical calculation (-0.07). The limits of agreements were approximately 0.5 and -0.7 in all methods, yet limits of agreement were narrowest with the Barrett and Haigis formulae. The predicted values derived from all other formulae provided a

general negative bias (<-0.2D), indicating that these formulae tend to underestimate values relative to effective addition power. Further correlation analysis confirmed that the predicted addition powers derived from the SRK/t and Barrett formulae demonstrated the least proportional bias when compared with the effective addition power, however, significant proportional bias was present on all Bland Altman plots.

3.7 Discussion

MIOL should be chosen to best suit the individual patients needs and lifestyle requirements (Davidson et al., 2016). In order to offer a personalised medicine approach consideration must be given to not only MIOL design but should also consider addition power, as the resultant near focal distance should be appropriate for a patient's needs. Previous literature has shown that the effective addition power at the spectacle plane can vary in individuals, and although manufacturers report the addition power at the IOL plane, the clinically relevant metric is the addition power achieved at the spectacle plane. (Davidson et al., 2016)This study explores the ability of IOL formulae to predict the effective addition power at the spectacle plane. Relative to the effective addition power, the predicted power derived from the Barrett formula demonstrated a similar mean, the highest correlation and the lowest proportional bias. These results suggest that the simple clinical technique for predicting addition power, as proposed in this paper, works best when using the Barrett formula. The Holladay, SRK/t and Hill RBF formulae tended to underestimate addition power.

There are fundamental differences in the measures included by the different IOL biometry formulae and these variations may partly explain the differences in predicted addition power observed. Both the Holladay and SRK/t formulae are based on thin lens vergence models using

only two parameters (AL and K) to estimate ELP (Holladay et al., 1988). Whereby, the Haigis, Barrett and Hill RBF formulae additionally incorporate measures of pre-operative anterior chamber depth (ACD). It is likely that the inclusion of ACD is an important factor for determining the addition power given that the forecast of post-operative ACD (ELP) is known to be the biggest source of error in IOL calculation and is likely to have undue influence on the addition prediction (Olsen, 1992, Olsen, 2007, Norrby, 2008). It is unclear as to why the Hill RBF proved to generate significantly different results from the effective power although being data driven and utilising pattern recognition may have influenced results.

A significant range of effective addition powers was found, ranging from 1.96D to 3.10D, this 1.14D variation amongst the subjects is likely to produce clinically significant differences in near vision. Petermeier's (Petermeier et al., 2009b) study found near working distance varied from 29.5cm to 34.6cm, equating to approximately 0.50D, however they do not quantify the effective addition power as such, simply the optimum near focal point from the defocus curve. Thus, we are unable to directly compare results. In a theoretical study, variations in near focal length of 53cm to 72cm with a +2.50D addition at the IOL plane, 44cm to 60cm with +3.00 addition and 33 to 44cm with +4.00D addition power at the IOL plane (Savini et al., 2016). These equate to 0.50 to 0.75D of variation in theoretical models, thus it is reasonable to see increase variation in our *in vivo* study compared to theoretical models.

Previous studies have compared MIOLs with addition powers (at the IOL plane) differing by ≤ 1.00D and found significant differences in vision at near and intermediate distance (Cillino et al., 2014, Kim et al., 2015). Such variation may influence patient satisfaction post-operatively as an individual may achieve a shorter or longer near working distance than would be ideally suited to their lifestyle.

It is possible to measure near focal point post-operatively without the use of defocus curves, however if measuring physical near focal length, then factors such as pupil constriction and convergence may enhance the near function, thus defocus assessment diminishes these pseudoaccommodation effects and should offer a more accurate reflection of addition power due to MIOL alone. In addition, to mitigate against the effects of uncorrected refractive error influencing near outcomes, defocus curves were plotted using best distance corrected refraction. Although near addition could be simply taken as the difference between maximum distance acuity and near acuity from a defocus profile, as we did in our calculation of simple effective addition, this limits the resolution to 0.50D, thus we believed fitting a spline curve to the data was advocated and suggest that this be the method of choice for future studies in addition power.

Despite our study population adhering to average eye metrics (K = 43.81D; AL = 23.65mm) reported by Hoffer(Hoffer, 1980) there was still considerable variation in the addition power achieved post-operatively, ranging from approximately 2.00 to 3.00D . This variation was not seen in the predicted addition power from the formulae. This narrower range of predicted addition powers resulted in significant negative proportional bias on the Bland Altman plots. The predicted addition powers from the Barrett and SRK/t formulae showed the least proportional bias. The mean predicted and effective additions were similar when using the Haigis and Barrett formula and both demonstrated a moderate correlation, yet only the Barrett was statistically significant.

Previous literature (Holladay and Hoffer, 1992) suggested an eye with a larger pre-operative ACD is likely to achieve a lower addition power than a fellow eye with a shallower ACD. Savini's theoretical study suggested that effective addition power should be highly predictable given AL, K and addition power at the IOL plane (Savini et al., 2016). It is likely that we see increased

variation in our results compared to these theoretical guidelines due to subjects not following such a conventional relationship, for example larger ACD in a shorter eye. However, we had insufficient variation in AL, K and ACD within our study group size to fully explore the effect of these factors and this warrants further *in vivo* studies.

3.8 Limitations

There are a number of limitations to this study. Despite the fitting of a spline curve to the data to improve resolution it is still somewhat limited by the 0.50 steps of the defocus curve, thus Reducing defocus step size to 0.25D would further improve the resolution of derived effective addition power. However, the resultant increase in assessment time may contribute to patient fatigue and diminish the reliability of the defocus data. To fully investigate the relationship between ocular biometry and effective addition power, a larger sample extending out with the normal range of axial length, corneal power and anterior chamber depth should be considered. This would also increase the range of base IOL powers investigated. This study also only included one MIOL power, and thus further in-*vivo* studies using a range of MIOLs is required.

3.9 Conclusion

The results of this study demonstrates that the effective addition power does vary between individuals and thus pre-operative prediction of expected addition power could be a useful tool for clinicians. The aim was to establish a simple clinical method for predicting post-operative addition power using IOL formulae, and although none of the formulae assessed were infallible, the Barrett II Universal was the most accurate predictor of effective addition power. The

proposed technique is simple to perform, it requires no additional assessments for the patient nor chair time and may have significant clinical value in screening for patients where ocular biometry may lead to aberrant addition power. Alternatively, it may be used to better match lifestyle requirements to the choice of MIOL addition, thus potentially reducing the risk of patient dissatisfaction post-operatively.

Thus in summary, the primary findings of this study are;

- Clinically significant variation exists in post-operative addition power at the spectacle plane
- The Barrett II Universal formula offers best prediction of post-operative addition power at the spectacle plane
- Further studies are required to fully evaluate factors influencing post-operative addition power

3.10 Supporting Publication

This Chapter forms the basis of the research paper:

Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **Exploring clinical methods for predicting the post-operative addition power of a multifocal intraocular lens at the spectacle plane.** *J Refract Surg*. Under Review

Chapter Four

A Randomised Controlled Trial comparing visual function and patient satisfaction following bilateral implantation of monofocal or bifocal intraocular lenses

OVERVIEW

Understanding the functionality and expected clinical outcomes of multifocal IOLs is fundamental for surgeons in order to provide an IOL that is appropriate to an individual's needs and to appropriately manage patient expectations, yet there are few randomised control trials available comparing multifocal to monofocal IOLs and no standardisation of methodology thus comparison between studies is difficult and often outcome measures which highlight the perceived disadvantages of MIOLs are not adequately assessed.

This study aimed to provide a randomised control trial utilising a robust methodology to allow rigorous examination of clinical and patient reported outcomes. In this study comparison was between a bifocal and monofocal IOL.

Our findings confirm improved near vision and spectacle independence in the multifocal group, and there was no inferiority of the multifocal in distance measures. In addition, despite the presence of dysphotopsia, there was no adverse effect on patient satisfaction.

4.1 Introduction

Multifocal intraocular lenses (MIOLs) are commonly used in cataract surgery and have been shown to provide good visual outcomes (Cillino et al., 2008, Alfonso et al., 2009b, Alio et al., 2012a, Ji et al., 2013, Santhiago et al., 2010). There are many different IOLs now available and extensive published material is available on both bench testing and clinical outcomes (de Silva et al., 2016, Gatinel and Loicq, 2016, Alio et al., 2018a, Alio et al., 2012a). Previous studies have found better unaided near vision in MIOLs compared to monofocal IOLs (Cillino et al., 2008, Harman et al., 2008) and thus they are widely considered to be the most reliable method of achieving spectacle independence following cataract surgery (Alio et al., 2018b, Alio et al., 2017, Greenstein and Pineda, 2017). Despite their reliability at achieving spectacle independence, MIOLs are known to have disadvantages such as reduced contrast sensitivity and the appearance halos and glare particularly in night vision (Cillino et al., 2008, Hayashi et al., 2009). The light energy distribution between focal points created by a MIOL influences the overall quality of vision at different viewing distances (Davison and Simpson, 2006). MIOLs that split light equal create focal points of comparative image quality, yet distance dominant lenses (where a higher percentage of light is directed towards the distance focal point) have a relative compromise of near image quality. As such, visual performance can vary dependent on the MIOL design chosen and also dependent on the addition power. Therefore, it is important that all available MIOLs are subject to rigorous assessments with a standardised protocol that can allow future non-partisan comparison with other MIOLs.

4.1.1 Standardisation of MIOL studies

As discussed in section **1.14**, there have been a number of Cochrane reviews examining the available literature on MIOLs, the most recent by de Silva in 2016 (de Silva et al., 2016). The

main aim was to establish whether MIOLs provide improved visual function comparable with a monofocal IOL despite the limiting factors inherent in MIOLs due to optical design. De Silva highlighted the need for further RCTs, and recommended they include a monofocal control (de Silva et al., 2016) .

The majority of previous RCTs examined by the Cochrane review team have typically evaluated subjects at 6 months or less post-operatively, and not all studies involved more than one study visit. Various authors have highlighted the need for longer term follow up (de Vries and Nuijts, 2013, Evans et al., 2020, Rosen et al., 2016, Wang et al., 2017). This is an important factor when considering the effects of photic phenomena which have been shown to diminish with time (de Vries et al., 2008) and contrast sensitivity which has been shown to improve with time (de Vries et al., 2008, de Vries et al., 2011, Kohnen et al., 2009).

4.1.2 Outcome Measures

The 2012 and 2016 reviews called for standardization of outcome measures in MIOL studies (Calladine et al., 2012, de Silva et al., 2016) . The review concluded that it was unclear from existing studies whether the achieved benefits of MIOL implantation i.e. greater near vision and increased spectacle independence, outweighed disadvantages such as reduced contrast sensitivity and increased dysphotopsia. Thus, it is imperative that near performance, contrast sensitivity, spectacle independence and patient perception of dysphotopsia are routinely assessed in MIOL studies. Subsequently others have also highlighted the importance of patient reported outcomes in MIOLs (Evans et al., 2020, Grzybowski et al., 2019). The inclusion of monofocal controls ensures that non-inferiority of MIOLs in standard post-cataract measures can also be ascertained, for example distance visual acuity and post-operative refraction (Mahmud et al., 2015).

4.1.3 MIOL selection

Previous RCTs included in the Cochrane Review had significant overlap in the MIOLs assessed, thus there are many MIOLs which have yet to been compared to a monofocal counterpart. As there have been few RCTs over the years comparing MIOLs to monofocals, many of the RCTs included in the Cochrane and systematic review are now considered older generation lenses and as such the current evidence base may now be considered outdated (Khandelwal et al., 2019). High addition MIOLs (+4.00D or higher) are the zeitgeist of the designs used in the late 1990s and early 2000s. However, disadvantages of these early MIOLs were their close near working distance. Moreover, halo size has been shown be larger with increasing addition power (Alba-Bueno et al., 2018, Vega et al., 2015) . Newer generation MIOLs have been shown to have better near vision and less dysphotopsia (Khandelwal et al., 2019) . This may be due to the lower addition powers now available.

The MIOL chosen for this study was the Bi-Flex MY MIOL has not previously been assessed in a randomised trial, nor has it been compared to a monofocal. The only published literature involving the Bi-Flex MY at the time of this study was a small cohort study (Garcia-Bella et al., 2018). The Bi-Flex MY, has a parent monofocal IOL using the same platform and thus provides an ideal comparator.

4.1.4 Study Aims

This study was designed to meet the recommendations of the Cochrane review to ensure a detailed insight into the visual performance of a MIOL. In addressing the main clinical outcomes highlighted in the Cochrane Review, this study aims to propose a robust methodology that could be repeated in the assessment of other MIOLs.

The present study compared the efficacy of the Bi-Flex MY MIOL over its parent monofocal, Bi-Flex 677AB IOL using a protocol incorporating a comprehensive range of previously published methodologies for assessing both visual function and the subjective perception of the quality of vision. In addition, where possible more than one method was used for the outcome measures to demonstrate repeatability, reliability and thus a rigorous examination of the visual performance of the lenses. Furthermore, all measures were assessed at two study visits, 3-6 months and 12-18 months post-operatively to ensure longer term effects of photic phenomena and patient satisfaction could be adequately assessed.

Therefore in summary, the aims of this study were:

- To provide a randomised controlled trial with a monofocal control group
- To utilise a robust methodology to allow rigorous examination and repeatability
- To include sufficient outcomes measures to ensure assessment of clinical performance is non-biased and patient reported outcomes are thoroughly considered.
- To allow comparison of two study visits, with sufficient follow up interval to assess long term visual function and satisfaction

4.2 Study Design

This study was a prospective, parallel double masked randomised clinical trial. The study protocol adheres to the Declaration of Helsinki and ethical approval was the South West Ethics board (Ref 15/SW/0027, IRAS 165928) obtained prior to commencement of the trial (Appendix

1). The study was registered with clinicaltrials.gov (NCT02338882) and written informed consent was obtained from all subjects. No modifications to the protocol or outcome measures were made during the study.

4.2.1 Patient Selection

Between September 2015 and May 2017, one hundred subjects were recruited from the routine NHS cataract clinics at the BMI Southend Hospital led by two consultant Ophthalmologists (RA and HK). The subjects were recruited on a consecutive – if – eligible basis according to the inclusion/exclusion criteria (Table 4.1). All subjects underwent initial examination by a consultant ophthalmic surgeon including dilated fundus examination: in the event of suspected macular pathology an OCT was carried out and if pathology was detected, the patient was excluded as per the study criterion. The anterior segment and ocular surface were also evaluated to confirm lack of pathology and minor ocular surface dryness was treated by commencement of ocular lubricants. Any ocular surface disease deemed moderate or marked resulted in exclusion.

Table 4.1: Inclusion/Exclusion Criteria	
Inclusion	**Exclusion**
Age related cataract requiring bilateral cataract surgery with phacoemulsification	Subjects with retinal pathology
Participants requiring primary IOL implantation	Previous intraocular and/or corneal surgery
Participants with a potential corrected visual acuity of 0.3 LogMAR or better on clinical assessment in both eyes	Subjects using a systemic medication that is known to cause ocular side effects
Subjects with clear intraocular media and normal anterior segment other than cataract	Subjects participating in a concurrent clinical trial or if they have participated in an ophthalmology clinical trial within the last 30 days
Participants aged 18+ years	Pregnant women
< 1.00D of preoperative corneal astigmatism	Subjects who could not make an informed consent

Subjects had the risks and benefits of surgery explained and the opportunity to ask questions. Eligible subjects who met the inclusion/exclusion criteria below, were provided with a verbal explanation of the study and further written information pertaining to the RCT issued for them to consider in their own time

The subjects were explicitly informed that the study was a randomised trial and therefore they may be implanted with either bilateral monofocal or bilateral multifocal IOLs. Consultants discussed the advantages and disadvantages of both monofocals and multifocals with the subjects at the initial consultation with particular emphasis given to contrast sensitivity, photic phenomena and spectacle dependence. Written information was also given to each potential subject. Written consent was obtained and consent forms recorded in the subject's medical record.

4.2.2 Randomisation and Masking

On enrolment, a study number was assigned to each subject. Using this study number, the allocation of lenses for all subjects was randomized in Microsoft Excel using blocked randomization with a 1:1 allocation ratio to guarantee that the distribution of IOL assignment was equal according to the first eye surgery. Consenting subjects were randomly assigned to one of two groups:

- bilateral implantation of the Bi Flex MY multifocal IOL
- bilateral implantation of the Bi Flex 677AB monofocal IOL

Following allocation of the subject number, the unmasked surgeons and theatre staff accessed the randomization log and a series of sealed opaque envelopes that described which lenses were to be implanted (MIOL or IOL). Throughout the study, only the operating surgeon and theatre nurse were unmasked and they took no part in the post-operative study assessment of the subjects. The allocation of IOLs was masked to both the participant and the investigator conducting the post-operative study assessments. The subjects were notified of their allocation once they had completed all study visits.

4.2.3 Intraocular Lenses

Each group had fifty subjects assigned. The Bi-Flex 677 AB (**Figure 4.1**) is a single piece, aspheric aberration neutral IOL. The material is a co-polymer of hydrophillic and hydrophobic acrylic, with 25% water content and a blue light filter (390nm to 470nm). The 6mm optic is biconvex and the lens has an overall length of 13mm. The lens has a relatively high Abbe number of 58 and thus low chromatic aberration. The Bi-Flex MY MIOL (**Figure 4.1**) has the same platform as the monofocal but the anterior surface has a 3mm apodized, diffractive central region (**Table 4.2**).

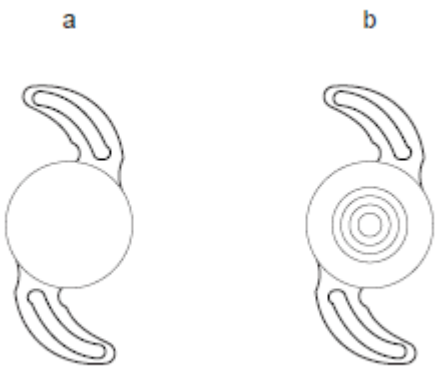


Figure 4.1: a. Bi-Flex 677AB b. Bi-Flex MY

Table 4.2: Characteristics of the Intraocular lenses

	Bi-Flex 677MY	Bi-Flex 677AB
Material	Copolymer of hydrophilic and hydrophobic acrylic	Copolymer of hydrophilic and hydrophobic acrylic
Blue Filter	390-470nm	390-470nm
Aspheric	Yes	Yes
Design	Diffractive Bifocal +3.50 Add	Monofocal
Refractive Index	1.46	1.46
Abbe	58	58
Range	0 to 30D (0.50D steps) 31 to 35D (1.00D steps)	-10 to 9D (1.00D steps) 10 to 30D (0.50D steps) 31 to 45D (1.00D steps)
Optic Diameter	6mm biconvex	6mm biconvex
Overall Length	13mm	13mm
Haptic	0.4 thickness with 0° angulation	0.4 thickness with 0° angulation
Estimated Incision Size	1.8 to 2.2mm	1.8 to 2.2mm
Pre-loaded	No	Yes

The Bi-Flex MY MIOL design is intended to provide distance dominance with greater mydriasis, thus maximizing contrast and minimizing halos when driving at night. Pupil miosis changes the light distribution relationship and results in a relatively equal split of light, hence, the Bi-Flex MY MIOL exploits the near miosis that occurs with reading. At the IOL plane, the near addition of the MIOL is +3.50D with the intent that intermediate vision is relatively preserved.

The Bi-flex platform haptic design has 0° angulation to facilitate the removal of the ophthalmic viscoelastic device and the design of the haptics allows for increased contact angle with the capsular bag. The lens has a 360° square edge for PCO prevention.

4.2.4 Study Funding

Funding support was received by Medicontur Medical Engineering (Zsámbék, Hungary). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

4.3 Surgical Technique

All surgeries were performed by one of two experienced consultant ophthalmic surgeons (RA and HK) using small incision phacoemulsification. The same surgeon implanted both lenses for an individual subject.

4.3.1 Pre-Surgery Medication

To achieve anaesthesia, Minims® Proxymetacaine hydrochloride 0.5% (Bausch & Lomb) eye drops were administered topically prior to and during surgery. In addition, topical application of the mydriatic agents, Minims® Tropicamide 1% (Bausch & Lomb) and Minims® Phenylephrine 2.5% (Bausch & Lomb) achieved pupil dilation. Oral administration of 250mg Acetazolomide was given routinely.

4.3.2 Surgical Technique

Surgery was performed by small incision phacoemulsification as detailed in Section 1.3.2, the OVD used was Hydroxypropyl Methylcellulose (HPMC) and both surgeons used a clear corneal incision of 2.2mm located according to the steepest corneal meridian. Finally, 1% cefuroxime was instilled intracamerally.

4.3.3 Post-Surgical Medication and Advice

Following surgery, the subjects were instructed to use Tobradex 3mg/ml/1mg/ml (Novartis) four times daily for four weeks following surgery. Standard post-operative advice was provided verbally and as an information leaflet.

4.3.4 Post-Operative Visit

Following surgery to their first eye, the subject was requested to attend a routine post-operative check one week after surgery. If no complications were identified then the subject was given a surgical date for the second eye within 3 weeks. Following second eye surgery the subject was asked to return for follow up 4 weeks post-surgery.

4.4 Method

The same masked investigator (EL) assessed the subjects at two study visits, 3-6 months (V1) and 12-18 months (V2) post-operatively. The same assessment room was used throughout the study with photopic light conditions of illuminance 120cd/m^2 and luminance of 95 lux. At each visit the same non-invasive tests were conducted and are summarised in Table 4.3.

Table 4.3: Clinical Measures		
	Outcome Measure	**Method**
Primary Outcome Measures	Subjective Refraction	6m LogMAR computerised Chart
	Distance Vision (UDVA) and VA (CDVA)	6m LogMAR computerised chart Monocular and Binocular
	Near Vision (UNVA) and VA (DCNVA)	40cm ETDRS Near Acuity Chart Monocular and Binocular
	Intermediate VA (DCIVA)	70cm ETDRS Near Acuity Chart Monocular and Binocular
	Defocus Curves (+1.50D to -5.00D in 0.50D steps)	6m LogMAR computerised Chart Monocular and Binocular
Secondary Outcome Measures	Contrast Sensitivity	Pelli-Robson 6m LogMAR computerised chart Monocular and binocular CSV-1000 2m chart Binocular
	Reading Speed	40cm Radner Reading Chart Binocular
	Visual Satisfaction Questionnaire	Subjective questionnaire
	NAVQ	Subjective questionnaire
	Glare	Simulator from Eyeland Designs
	Biometry	LenStar

4.4.1 Refraction

A combination of objective and subjective techniques were used to determine the residual refractive error. Retinoscopy was conducted using the Keeler professional Retinoscope (Keeler Ltd, Windsor, UK). Standard subjective refraction was conducted using the Thomson Test Chart 2000 (Thomson Software Solutions, Hatfield, Herts, UK). The distance focal point was the target in all subjects. This distance refraction was then used for all measures which required the subject to be best distance corrected. For all participants, manifest spherical equivalent (MSE) was calculated and astigmatism was analysed using the power vector method as described by Thibos (Thibos et al., 1997). The effect of uncorrected astigmatism is known to be detrimental to outcomes and as such vector analysis was used to ensure that astigmatic effect was considered appropriately.

4.4.2 Visual Acuity

At each visit, monocular and binocular LogMAR acuities for unaided distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) were measured using the Thomson Test Chart 2000 at 6m. The chart follows the Bailey-Lovie principles and employs Sloan letters consistent with testing methods established by the Early Treatment Diabetic Retinopathy Study (ETDRS) (Ferris et al., 1982, Hazel and Elliott, 2002, Rosser et al., 2003, Shah et al., 2010, Williams et al., 2008). Since their advent, ETDRS charts have been the gold standard of VA testing (Ferris et al., 1982). Williams and colleagues called for uniformity in VA measurements in published material (Bourgogne et al., 2008, Williams et al., 2008). These standardised charts allow easily repeatable measures with no conversion of VA required. The assessment of unaided near visual acuity (UNVA), distance corrected near visual acuity (DCNVA) and distance corrected intermediate visual acuity (DCIVA) utilised ETDRS charts for near (40cm) and intermediate (70cm) (LogMAR Chart 2000, Precision Vision TM, La Salle, IL, USA) working distances respectively. It must be noted that other studies have considered the patient preferred reading distance (Blaylock et al., 2006, Santhiago et al., 2010), however an arbitrary distance was chosen in this study as the primary aim was comparison with a monofocal control group.

4.4.3 Defocus Curve

To further assess intermediate and near vision, defocus profiles were plotted. Defocus curve profiles (visual acuity over imposed defocus) were assessed monocularly and binocularly for each subject over a defocus range of +1.50D to -5.00D in 0.50D steps as described previously in Section 2.6.1 and in accordance with the previously published methodologies (Gupta et al., 2007, Gupta et al., 2008, Wolffsohn et al., 2013).

4.4.4 Contrast Sensitivity

Two different methods of evaluating contrast sensitivity were used on each subject. The Pelli-Robson Contrast Sensitivity chart uses triplets of letters gradually reducing in contrast. The chart was developed by Pelli and Robson to introduce a method of contrast sensitivity testing that did not rely on sinusoidal gratings and was analogous to standard visual acuity testing methods in order for it to be utilised in routine clinical testing (Pelli, 1988). The letters remain of constant size throughout the test but the contrast of each subsequent triplet is reduced by a factor of $1/\sqrt{2}$. The subject's threshold is taken to be the lowest contrast at which at least 2 letters are correctly identified. The Pelli-Robson chart available on the Thomson Chart 2000 was used to enable the letters in each triplet to be randomised to allow for monocular and binocular testing without the subject memorising the letters.

Additionally, contrast sensitivity was assessed binocularly with the CSV-1000 (Precision Vision TM, La Salle, IL, USA) calibrated to 2.4m The CSV-1000 presents 4 spatial frequencies (3, 6, 12 and 18 cycles/degree), each on an individual row on the chart. Vertical pairs of gratings of diminishing contrast are show where each pair comprises one blank patch and one grating patch.

The contrast threshold is determined by way of three choices; "top", "bottom" or "both blank". The subject is encouraged to say if both grating appears blank and thus not to guess in a forced choice model.

4.4.5 Reading Speed

It is relatively simple to measure near visual acuity clinically however; reading speed is known to align more closely with an individual's ability to perform near tasks. (Gupta et al., 2009) Reading acuity, critical print size and maximum reading acuity were assessed using the Radner

reading charts. The Radner charts use standardised sentence optotypes. Each sentence has 14 words of comparable length and lexical difficulty, over three lines using 82 -84 characters. (Radner et al., 1998). Each sentence consists of 20 syllables and equates to 0.1 LogRAD.

Reading speed was measured using a stopwatch allowing measurement in seconds to two decimal places; this method has been found to show good inter-examiner repeatability (Radner et al., 2017). A recent study found that although new automated computer programmes provide a reliable method of measuring reading speed, utilising a simple stopwatch was still a reliable method although there are several possible sources of inaccuracy (Radner et al., 2017). Critical print size was calculated and defined as the smallest print size where maximum reading speed can be maintained (Radner et al., 1998). The smallest print size that could be read by the subject was documented as Radner acuity.

4.4.6 Visual Satisfaction Questionnaire

A self-developed quality of vision questionnaire (QoV) was used to determine the subject's overall satisfaction with their vision. The questionnaire asked the subject to grade their satisfaction of their visual outcomes since surgery and provide an assessment of ease/difficulty of everyday tasks, near vision tasks by grading it on a Likert scale (1 = easy to 7 = very difficult). There were also asked a series of questions pertaining to night vision and photic phenomena. This questionnaire is not validated but was previously used in another multifocal study (Law et al., 2014)(Appendix 2).

4.4.7 Near Assessment Visual Questionnaire (NAVQ)

The NAVQ is a validated questionnaire designed to specifically assess the subjective near vision satisfaction following presbyopic correction (Buckhurst et al., 2012a). It is known to have high test-retest reliability and it uses a Rasch analysis led scoring system. Rasch analysis has become the standard technique for validating questionnaires (de Boer et al., 2004) A recent study established it to be a leading questionnaire for assessing quality of life after refractive surgery (Kandel et al., 2017).

4.4.8 Glare Simulator

The assessment of visual disturbances/photic phenomena varies throughout the literature, and this may be the reason why the evidence for incidence and severity of haloes with differing MIOLs is equivocal (Buckhurst et al., 2017). Previously published literature often uses questionnaires only to establish the occurrence of visual disturbances and thus are unable to quantify the size of any visual disturbance (Cochener and Concerto Study, 2016, Maurino et al., 2015). It is likely that responses are dependent on whether questions are direct/indirect and open or closed (Mendicute et al., 2016). Some authors have asked subjects to view a series of photographic images, choosing the closest match to their perception or attribute a difficulty score to each image (Garcia-Bella et al., 2018, Hunkeler et al., 2002, McAlinden et al., 2010). Whereas, others have used objective measurements such as halometers (Allen et al., 2009, Buckhurst et al., 2017, Pieh et al., 2001). In this study, the subjects were shown the Halo and Glare Simulator (Eyeland Design Network, GmbH, Vreden, Germany) in order to assess the type, size and brightness of dysphotopsia present at each visit, we also included questions pertaining to dysphotopsia in our QoV questionnaire. The simulator has previously been used

in many other studies investigating a variety of IOLs (Darian-Smith and Versace, 2020, Giers et al., 2019, Kretz et al., 2015b, Savini et al., 2018b, Son et al., 2019).

The simulator displays an image on a computer display of a road scene at night (**Figure 4.2**).

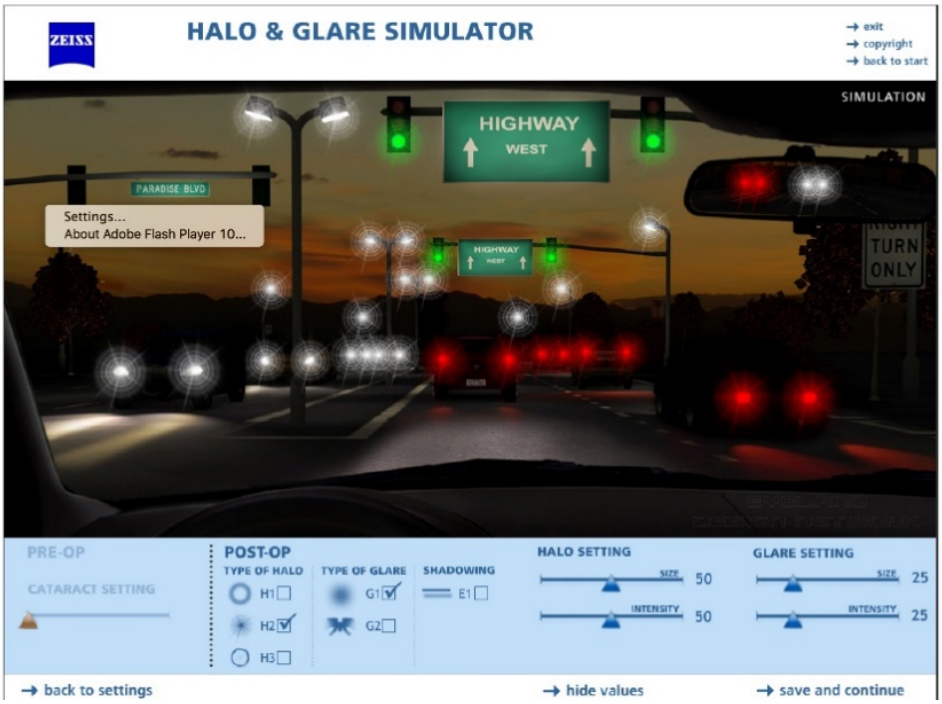


Figure 4.2: Halo & Glare Simulator

Light sources in green, red and white are pictured and the subject is able to alter the size and intensity of halos and glare independently around the light sources on a sliding scale from 0 (nil) to 100 (maximum) with the aim of creating an image on screen that best represents their experience of halos/glare. They are also able to choose for 3 halo styles (**Figure 4.3**) and 2 glare types (**Figure 4.4**). Size and intensity for both halos and glare are given a score (0 to 100), to allow comparison inter and intra-subject and this will allow comparison with other studies using the simulator for different lenses (Kretz et al., 2015a).

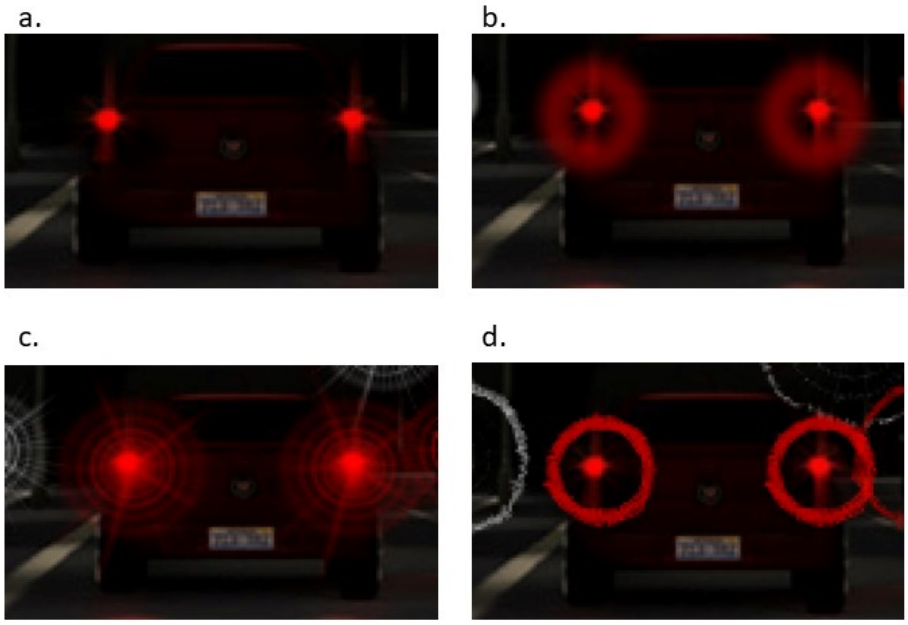


Figure 4.3: Halo Style

a. No halo
b. Halo style 1 (H1)
c. Halo style 2 (H2)
d. Halo style 3 (H3)

Figure 4.4: Glare Type

a. No glare
b. Glare type 1 (G1)
c. Glare type 2 (G2)

4.5 Statistical Analysis

Statistical analysis was performed using SPSS software, version 24 (SPSS Inc, IBM, Armonk, NY, USA). Details of specific statistical analysis used for each measure follow below. In all cases, a

p value <0.05 was considered statistically significant. In order to evaluate effect size, Cohen's d was calculated, with d >0.2, 0.5 and 0.8 corresponding to small, medium and large effect sizes, respectively.

4.5.1 Sample Size

The sample size for the study was calculated using G*power3 (Heinrich Heine, University of Dusseldorf, Germany) (Faul et al., 2007). Power calculations were based on a medium effect size (f = 0.30) based on *a-priori* matched pairs *t test* design and a desired statistical power of 90% with an error probability of 0.05. A minimum of 90 subjects were required for this study, hence to allow for dropouts, 100 subjects were recruited.

4.5.2 Assumption of Normality

In order to test the distribution of the data, visual examination of histogram plots and the Shapiro-Wilks test was used. Parametric testing was used if the data followed a normal distribution, whilst if the data did not follow a normal distribution, non-parametric analysis was used.

4.5.3 Comparison of Eyes

A two-way repeated measures ANOVA was performed to determine differences between the right and left eyes of subjects. As both eyes were found to be similar then only right eye data was presented for monocular measures (Ray and O'Day, 1985).

4.5.4 Patient Demographics

Independent *t*-tests were used to check for similarities in the patient demographics.

4.5.5 Refraction

Manifest spherical equivalent (MSE) was calculated according to Equation 4.1, thereafter dependent *t* tests were used to compare individual subjects between visits and independent *t* tests to compare groups

$$MSE = Sphere + \frac{1}{2} cylinder\ power$$

Equation 4.1: Manifest spherical equivalent

Cylindrical effect was converted using Equation **4.2** and **4.3** to allow vector analysis of the astigmatic effect (Thibos et al., 1997).

$$J_0 = J \cos 2\alpha$$

J_0 = cylindrical effect at 180°
J = cylindrical power
a = axis in radians

Equation 4.2: Calculation of J_0

$$J_{45} = J \sin 2\alpha$$

J_{45} = cylindrical effect at 45°
J = cylindrical power
a = axis in radians

Equation 4.3: Calculation of J_{45}

4.5.6 Visual Acuity and Contrast Sensitivity

A mixed ANOVA were utilised to determine differences between groups for all visual acuity measures, Pelli Robson and CSV-1000 contrast sensitivity testing. Repeated measures ANOVA were used to ascertain differences within groups with monocular and binocular measures. Where significant difference were found, post hoc testing was used to establish the pairwise differences.

4.5.7 Defocus Curves

Three methods were used to describe the defocus curves; direct comparison, area of focus curve and range of focus. These methods were discussed in detail in Chapter 2.

4.5.7.1 Correction for spectacle magnification

A thin lens calculation using BVD = 12mm, was applied to all defocus data to correct for spectacle magnification (Equation 2.2)

4.5.7.2 Direct Comparison of defocus curves

A two-way repeated measures ANOVA was utilised to check for differences between right and left monocular defocus curves and between monocular and binocular defocus curves. A further one-way ANOVA was used, as required, and Bonferroni *post-hoc* tests to establish pairwise differences.

4.5.7.3 Curve fitting to defocus

MatLab R2017b (The Mathworks Inc, Natick, MA, USA) was used to fit a cubic spline curve to the defocus data in accordance with the methods previously described in Chapter 2.

4.5.7.4 Area of Focus

Integration of the fitted cubic spline curve was performed so that the area of focus (AoF) metric (LogMAR*m^{-1}) could be derived. In order to determine the area under the defocus curve, a limit of y = 0.3LogMAR was set as this is the UK, European and American binocular visual acuity driving standards (Bron et al., 2010, Rees, 2015). The boundaries on the x- axis were set by divided into 3 specific areas. Distance was defined as (-0.5 to +0.5 defocus), intermediate (-0.5 to -2.0D defocus) and near (-2.0 to -4.0D defocus) according to the Buckhurst protocol (Buckhurst et al., 2012b).

A two-way repeated measures ANOVA was used to determine any differences between monocular and binocular defocus at both visits and mixed ANOVA was used to assess between groups. *Post hoc* pairwise testing was applied where differences were found.

4.5.7.5 Range of focus

Range of focus is defined as the dioptric range where a subject could sustain a minimum visual acuity. This was set at 0.3 LogMAR again to coincide with the UK driving standards (Bron et al., 2010, Rees, 2015). Curve fitting allowed any sections where VA dropped below 0.3 within the total range of focus to be excluded as this is referred to as actual range of focus.

4.5.8 Radner Reading Speed

Reading speed was calculated according to **Equation 4.4**.

$$Reading\ Speed\ (wpm) = \frac{60\ (14 - e)}{t}$$

t= time taken to read each sentence (s)
wpm = words per minute
e = number of errors made

Equation 4.4: Calculation of reading speed

A non-linear regression curve, exponential rise to maximum, was fitted to the reading speed data (**Figure 4.5**) using SigmaPlot Version 13.0 (Systat Software Inc, San Jose, CA, USA). Maximum reading speed (MRS) was defined as the asymptote of this curve and Critical print size (CPS) was calculated as the value for x (print size) when the reading speed was 95% of the MRS. Repeated measures ANOVA was used to compare the data between groups.

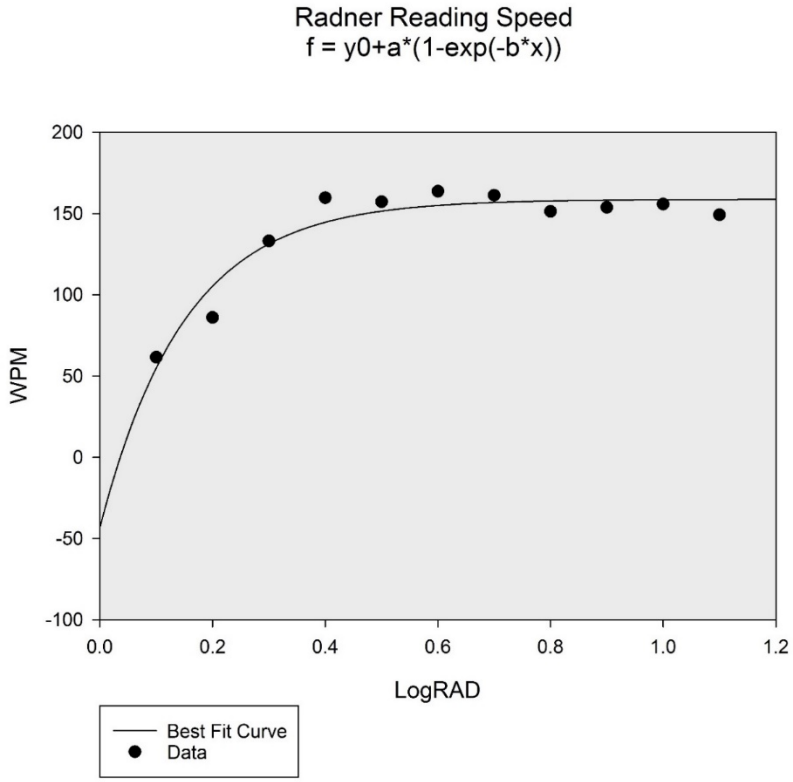


Figure 4.5: Example of non-linear regression curve fitting to reading speed data

4.5.9 Questionnaire

Conversion of the NAVQ results to a Rasch score allowed significance to be determined with a Wilcoxon rank-sum test.

4.5.10 Halo and Glare Simulator

The scores for each individual were collated and the size and intensity scores were compared between groups over both visits using a mixed ANOVA with *post hoc* pairwise testing where differences were found.

4.6 Results

This study is reported in alignment with the CONSORT statement recommendations for reporting of a RCT (Moher et al., 2010).

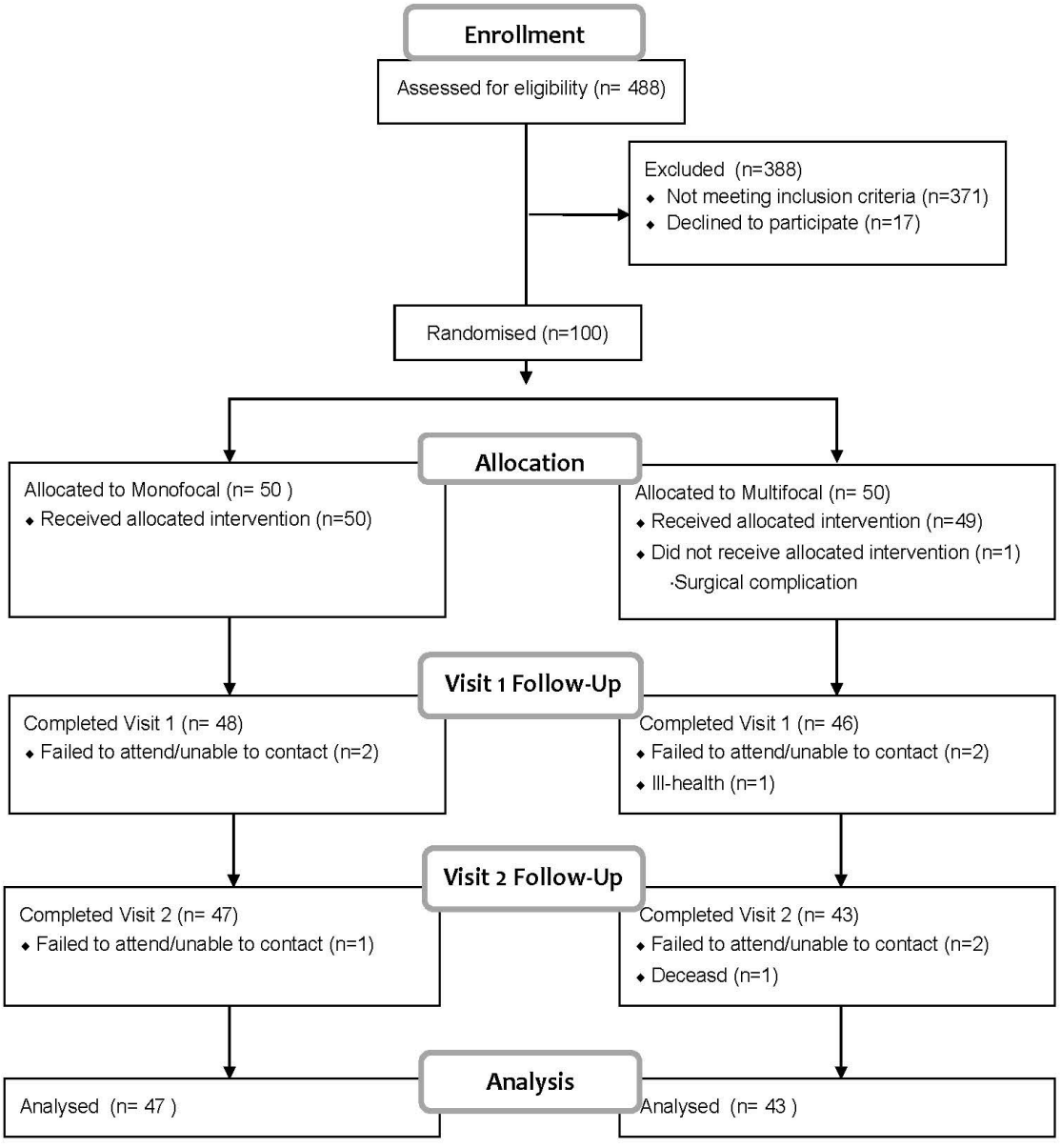


Figure 4.6: CONSORT Trial Flow Diagram

4.6.1 Patient Demographics

Four hundred and eighty-eight potential subjects were assessed in the routine cataract clinic (Figure 4.6), 76 % were excluded as they failed to meet the inclusion/exclusion criteria. A further 3.4% met the criteria but declined to participate. The remaining 100 subjects were recruited to the study. Ninety subjects completed the full study, one subject (allocated to the multifocal group) had a surgical complication (posterior capsular rupture) prior to IOL insertion and thus was excluded from the study. The subject was notified of the complication in line with Duty of Candour protocols and reasons given for their withdrawal from the study. All remaining ninety-nine subjects attended initial post-operative assessment with the consultant ophthalmic surgeon 3-4 weeks post-surgery, however 9 subjects were lost to follow-up thereafter. One subject was unable to attend due to ill – health, another died between visit 1 and visit 2, the remaining 7 failed to attend study visits despite repeated efforts to contact them (Figure 4.6). There were no adverse or serious adverse events reported in any of the study participants.

Ages were similar between groups ($F = 0.670$, $p = 0.96$). There were more females than males in both groups. There were no significant differences in pre-operative measures between subjects in the monofocal IOL and MIOL groups, $p > 0.05$ in all instances (Table 4.4).

Table 4.4: Patient Demographics			
	Monofocal	Multifocal	*p*
Number of subjects	47	43	
Male/Female	36% / 64 %	22% / 78%	
Mean Age (yrs)	76.7 ± 6.4	76.6 ± 6.1	0.96
Range (yrs)	58 – 88	57 - 90	
Pupil Size	3.71 ± 0.53	3.75 ± 0.62	
Pre-Op Refractive Error (DS)			
Spherical Equivalent Range	-6.80 to +3.50	-5.62 to +5.40	
MSE	0.09 ± 2.02	-0.46 ± 2.48	0.25
J0	0.60 ± 0.77	0.65 ± 0.69	0.76
J45	0.02 ± 0.45	0.04 ± 0.50	0.80
***Emmetrope**	21%	20%	
***Myope**	30%	44%	
***Hyperope**	49%	36%	
Pre-Op Visual Acuity (logMAR)			
R CDVA	0.32 ± 0.12	0.36 ± 0.14	0.17
IOL Power (D)			
Range	8 to 26.5	13 to 30	
Mean	21.1 ± 3.5	20.9 ± 3.2	0.85
*Emmetropia defined as +0.50 to -0.25, Hyperopia >0.50, Myopia >-0.25 CDVA = Corrected distance visual acuity, IOL = Intraocular lens, J0 = cylindrical effect at 180°, J45 = cylindrical effect at 45° ,MSE = Manifest spherical equivalent Data are mean ± Standard deviation			

4.6.2 Post-Operative Refraction

For all participants, manifest spherical equivalent (MSE) was calculated and astigmatism was analysed using the power vector method as described by Thibos (Thibos et al., 1997). The effect of uncorrected astigmatism is known to be detrimental to outcomes and as such vector analysis was used to ensure that astigmatic effect was similar between groups (Wolffsohn et al., 2011). No significant differences were found between groups ($p > 0.05$) (**Table 4.5**).

Table 4.5: Refraction			
	Monofocal	Multifocal	*p*
Visit 1			
Right Eye MSE	-0.01 ± 0.48	0.01 ± 0.40	0.85
J0	0.35 ± 0.53	0.40 ± 0.51	0.69
J45	0.05 ± 0.24	0.01 ± 0.14	0.37
Visit 2			
Right Eye MSE	0.05 ± 0.41	0.05 ± 0.40	0.95
J0	0.39 ± 0.00	0.42 ± 0.54	0.63
J45	0.06 ± 0.32	-0.03 ± 0.30	0.14
MSE = manifest spherical equivalent, J0 = cylindrical effect at 180°, J45 = cylindrical effect at 45° Data are mean ± standard deviation			

4.6.3 Visual Acuity

Visual acuity was assessed monocularly and binocularly in all subjects

4.6.3.1 Visual Acuity within groups

Repeated measures ANOVA compared right eye, left eye and binocular VA data was compared within the monofocal group ($F_{2,12}$ =3.158, p <0.01) and the multifocal group ($F_{2,12}$ = 3.171, p <0.01). Further univariate analysis with *post hoc* testing found no significant differences between right and left eye data. Similar results were found between V1 and V2 (Monofocal $F_{1,8}$ = 0.300, p = 0.099)(Multifocal $F_{1,8}$ = 0.591, p = 0.447). However, significant differences between monocular and binocular data for UDVA (p = 0.004) and CDVA (p = 0.007) were found at V1. At V2 there was a significant difference only with UDVA (p <0.001) between monocular and binocular data in the monofocal group.

In the multifocal group there were also differences between UDVA (V1, p = 0.002)(V2, p = 0.003) and CDVA (V1, p =0.036)(V2, p = 0.03) when monocular and binocular data were compared at both visits.

4.6.3.2 Visual Acuity between groups

Significant differences were found for UNVA ($p < 0.01$) and DCNVA ($p < 0.01$) were found both monocularly and binocularly at V1 and V2, with near visual acuity being significantly better in the MIOL group. No significant difference was found for intermediate vision (70cm) (**Figure 4.7**)(**Table 4.6**).

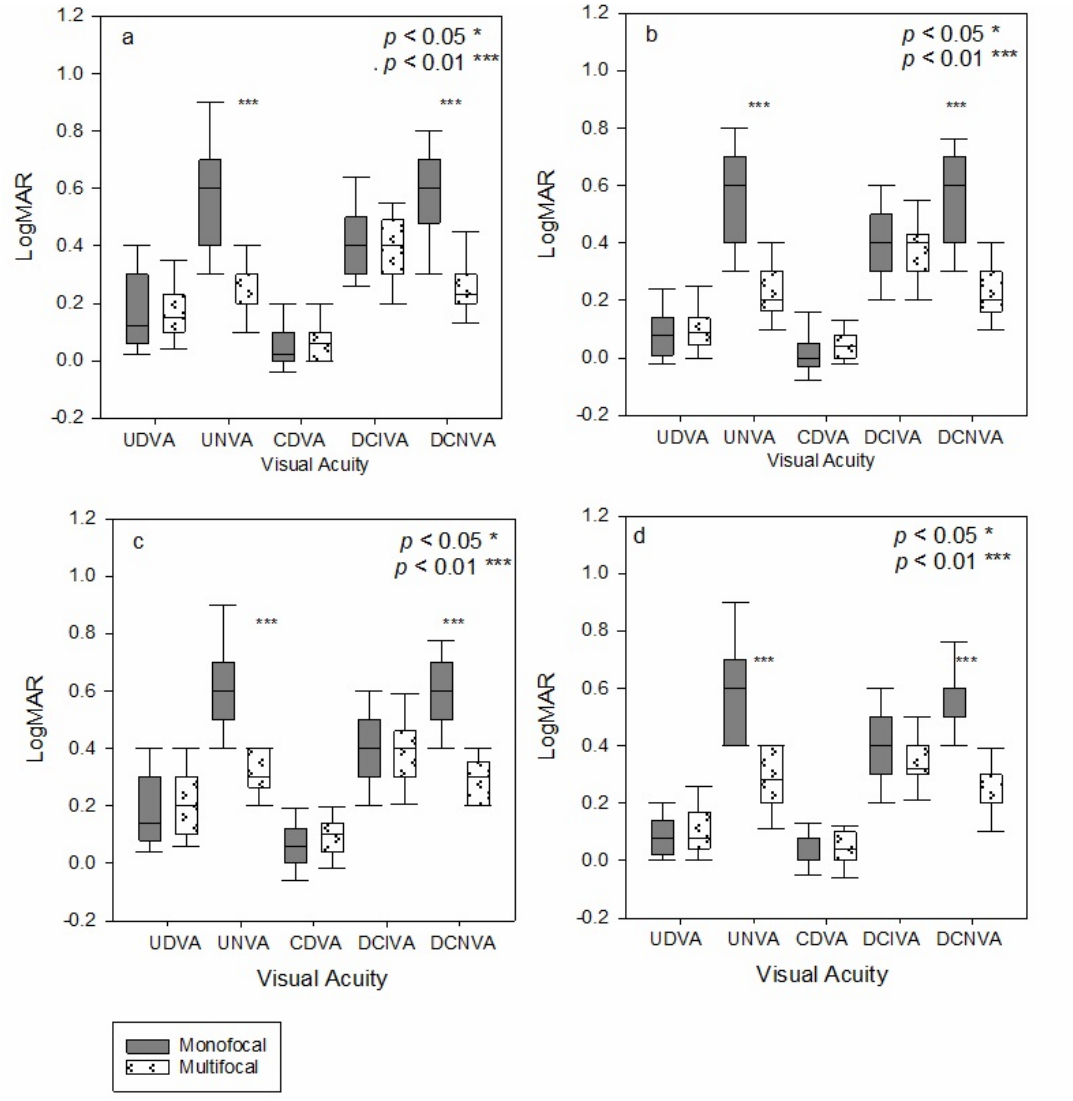


Figure 4.7: Visual Acuity. Error bars = standard deviation

a.Visit 1 Monocular Visual Acuity
b. Visit 1 Binocular Visual Acuity
c. Visit 2 Monocular Visual Acuity
d. Visit 2 Binocular Visual Acuity

Table 4.6: Visual Acuity Results

	Monofocal	Multifocal	95% CI of the difference		*p*	Cohen's d
			Lower	Upper		
Visit 1Monocular						
UDVA	0.171 ± 0.144	0.183 ± 0.156	-0.069	0.055	0.818	0.080
UNVA	0.576 ± 0.211	0.276 ± 0.160	0.229	0.382	<0.01	1.330
CDVA	0.052 ± 0.083	0.076 ± 0.077	-0.052	0.174	0.321	0.167
DCIVA	0.417 ± 0.134	0.393 ± 0.125	-0.024	0.087	0.261	0.185
DCNVA	0.571 ± 0.180	0.271 ± 0.132	0.241	0.373	<0.01	1.901
Visit 1 Binocular						
UDVA	0.085 ± 0.105	0.101 ± 0.085	-0.049	0.032	0.696	0.167
UNVA	0.554 ± 0.197	0.231 ± 0.125	0.259	0.395	<0.01	1.958
CDVA	0.012 ± 0.072	0.044 ± 0.064	-0.054	0.070	0.136	0.470
DCIVA	0.391 ± 0.128	0.378 ± 0.132	-0.037	0.074	0.509	0.100
DCNVA	0.535 ± 0.170	0.236 ± 0.131	0.235	0.366	<0.01	1.970
Visit 2Monocular						
UDVA	0.192 ± 0.156	0.205 ± 0.138	-0.076	0.051	0.692	0.085
UNVA	0.614 ± 0.198	0.319 ± 0.107	0.227	0.363	<0.01	1.854
CDVA	0.070 ± 0.105	0.093 ± 0.090	-0.065	0.191	0.281	0.235
DCIVA	0.421 ± 0.180	0.389 ± 0.130	-0.035	0.100	0.352	0.204
DCNVA	0.605 ± 0.133	0.288 ± 0.143	0.257	0.376	<0.01	2.296
Visit 2 Binocular						
UDVA	0.093 ± 0.092	0.102 ± 0.100	-0.051	0.032	0.602	0.094
UNVA	0.574 ± 0.178	0.275 ± 0.103	0.236	0.362	<0.01	2.056
CDVA	0.031 ± 0.078	0.039 ± 0.070	-0.039	0.025	0.356	0.107
DCIVA	0.393 ± 0.165	0.354 ± 0.103	-0.021	0.098	0.431	0.284
DCNVA	0.571 ± 0.137	0.241 ± 0.100	0.278	0.382	<0.01	2.751

CDVA = corrected distance visual acuity, CI = confidence interval, DCIVA = distance corrected intermediate visual acuity, DCNVA = distance corrected near visual acuity, UDVA = unaided distance visual acuity, UNVA = unaided near visual acuity acuity
Data are mean ± standard deviation
Cohen d > 0.2 = small effect size, Cohen's d > 0.5 = medium effect size, Cohen's d > 0.8 = large effect size

4.6.4 Defocus

In direct comparison of the defocus data, significant differences found ($F_{1,42}$ = 131.889 p < 0.01). Pairwise comparisons identified that the differences were significant through the defocus range -2.00 to -5.00 (p < 0.01) at both visits, monocularly and binocularly (**Figure 4.8**). Cohen's D effect size was calculated and remained > 1 throughout this range, thus categorized as a large effect size. Monocular and binocular defocus curves were compared, ($F_{2,42}$ = 98.427,

p <0.01). *Post hoc* tests, showed similarity with right and left eyes (*p* = 0.971) but VA was significantly better with binocular defocus (*p* < 0.01).

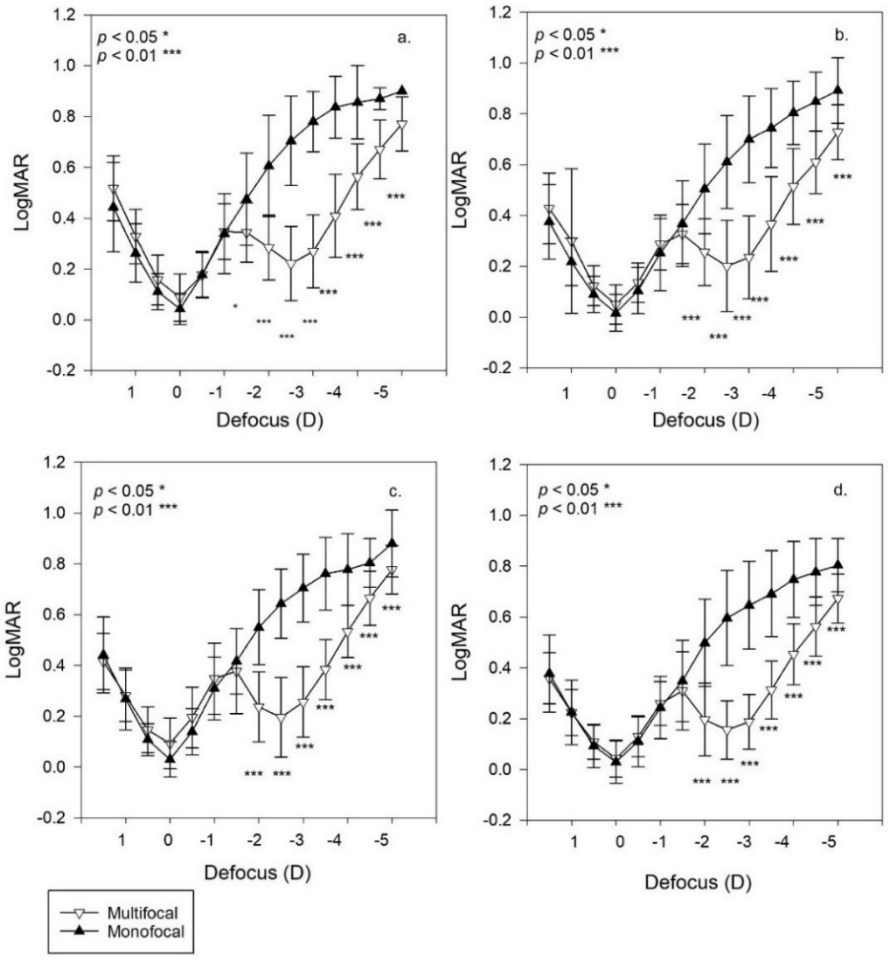


Figure 4.8: Defocus Profiles. Error bars = standard deviation

a. Visit 1 Monocular Defocus Curve
b. Visit 1 Binocular Defocus Curve
c. Visit 2 Monocular Defocus Curve
d. Visit 2 Binocular Defocus Curve

Defocus curves were also analysed using the area of focus method as previously described (Buckhurst et al., 2012b). Distance area was significantly greater in the monofocal group at V1 but not at V2, no difference was found in the intermediate area but the MIOL group showed a larger near area at both visits (Figure 4.7, Table 4.8). In addition to the area metrics, range of focus was calculated as the dioptric range where VA was ≥ 0.3 LogMAR, by finding the roots of

the spline curve fitted. The MIOL group had a significantly larger range of focus (p<0.001) (Figure 4.9 c and 4.9d, Table 4.7).

Table 4.7: Area of Focus

	Monofocal	Multifocal	95% CI of the difference		*p*	*Cohen's d*
			Lower	Upper		
Visit 1						
Area Distance	0.259 ± 0.068	0.218 ± 0.078	0.006	0.067	0.021	0.560
Area Intermediate	0.096 ± 0.086	0.089 ± 0.065	-0.024	0.039	0.653	0.092
Area Near	0.001 ± 0.009	0.151 ± 0.144	-0.192	-0.106	<0.01	1.897
Range of Focus	2.568 ± 0.633	3.735 ± 1.129	-0.6172	-1.444	<0.01	1.275
Visit 2						
Area Distance	0.246 ± 0.077	0.228 ± 0.069	-0.015	0.050	0.285	0.246
Area Intermediate	0.108 ± 0.091	0.121 ± 0.080	-0.050	0.025	0.513	0.152
Area Near	0.002 ± 0.006	0.199 ± 0.123	-0.236	-0.157	<0.01	2.262
Range of Focus	2.565 ± 0.774	4.144 ± 1.109	-2.072	-1.259	<0.01	1.651

Data are mean ± standard deviation
Cohen d > 0.2 = small effect size, Cohen's d > 0.5 = medium effect size, Cohen's d > 0.8 = large effect size
Distance 0.5 to -0.5D, Intermediate -0.5 to -2.00D and Near -2.00 to -4.00D

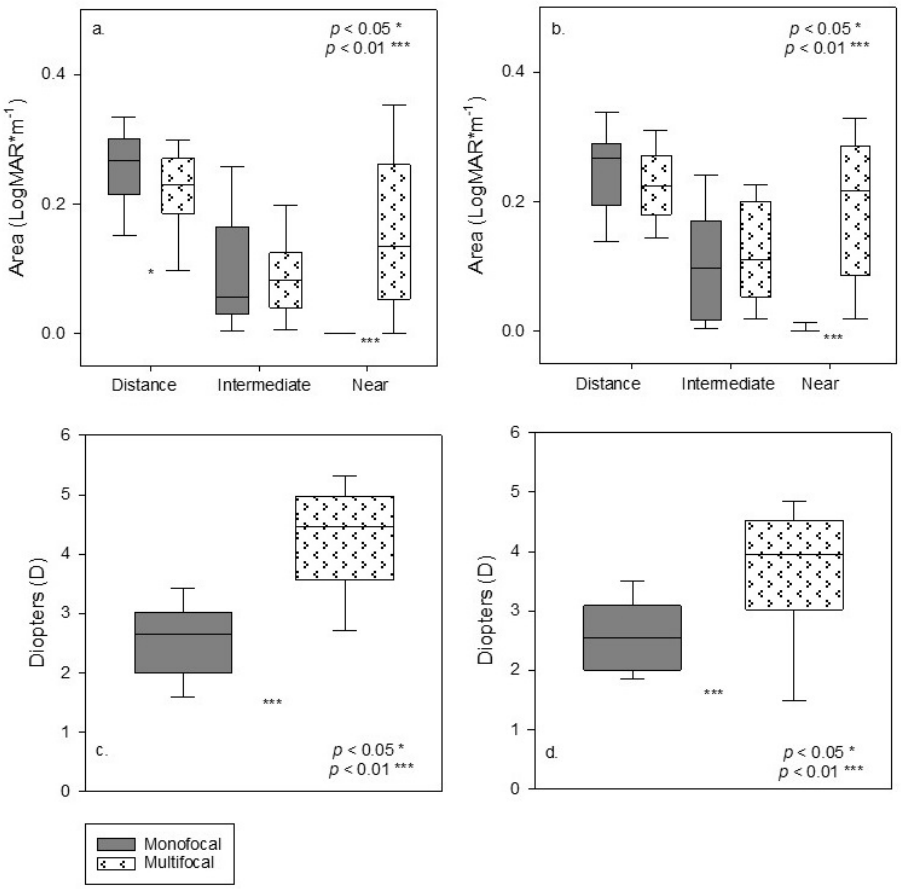


Figure 4.9: Area of Focus and Range of Focus Defocus Metric. Error bars = standard deviation

a. Visit 1 Area under defocus curve
b. Visit 2 Area under defocus curve
c. Visit 1 Range of focus
d. Visit 2 Range of focus

4.6.5 Reading Speed

There was significantly better critical print size (CPS) and reading acuity achieved in the MIOL group at V1 ($p < 0.01$) and V2 ($p< 0.01$). No significant difference in MRS was found between groups at either visit ($p = 0.534$ V1 and $p = 0.555$ V2).

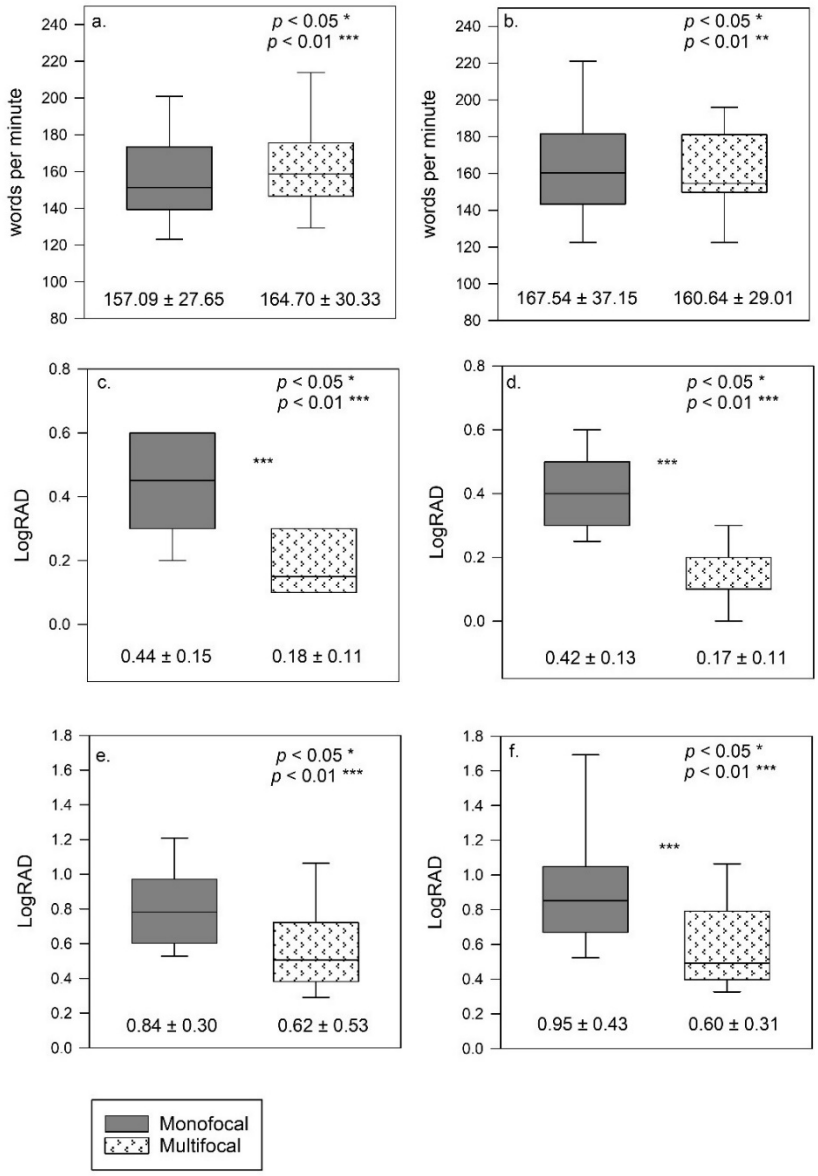


Figure 4.10: Radner reading assessment. Error bars = standard deviation

a. Visit 1 Maximum Reading Speed
b. Visit 2 Maximum Reading Speed
c. Visit 1 Reading Acuity
d. Visit 2 Reading Acuity
e. Visit 1 95% Critical Print Size
f. Visit 2 95% Critical Print Size

4.6.6 Contrast Sensitivity

Monocular and binocular measures of contrast sensitivity with the Pelli-Robson charts showed a significantly better CS measure binocularly within both groups (Monofocal F = 7.558, p < 0.01, Multifocal F = 5.291, p < 0.01). Between groups the difference in CS was significant both binocularly and monocularly (p <0.01) at V1 with a large effect size demonstrated (Cohen's d = 0.845 and 1.031 respectively). However, at V2, there was no significant difference between groups when tested binocularly (p = 0.059), although monocular differences remained (p < 0.001).

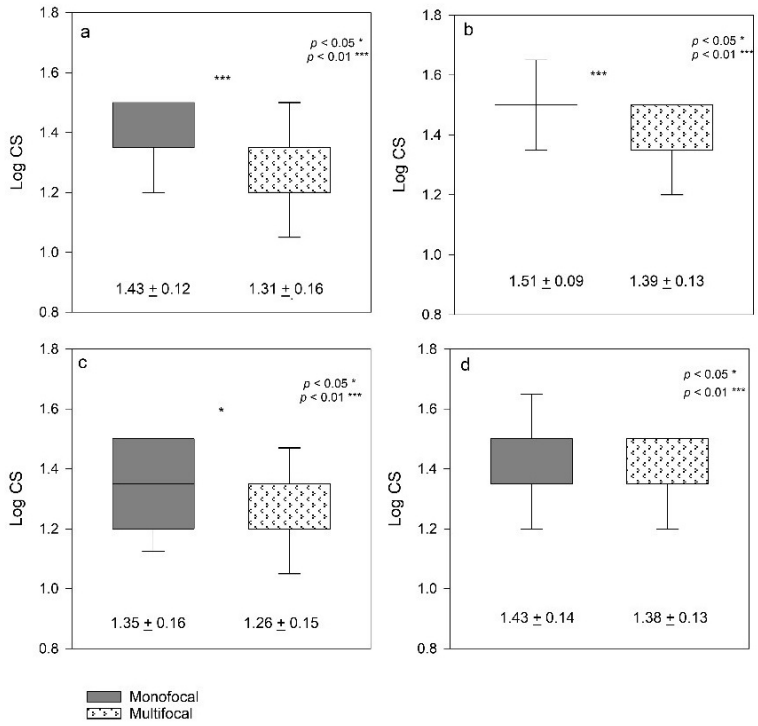


Figure 4.11: Pelli Robson Contrast Sensitivity. Error bars = standard deviation

a. Visit 1 Monocular Contrast Sensitivity
b. Visit 1 Binocular Contrast Sensitivity
c. Visit 2 Monocular Contrast Sensitivity
d. Visit 2 Binocular Contrast Sensitivity.

Binocular CS, measured with the CSV-1000, was greater in the monofocal IOL group at visit 1 when measured at 3, 6 and 12cpd spatial frequencies; this difference was only present for 12 and 18cpd at Visit 2 (Figure 4.12, Table 4.8).

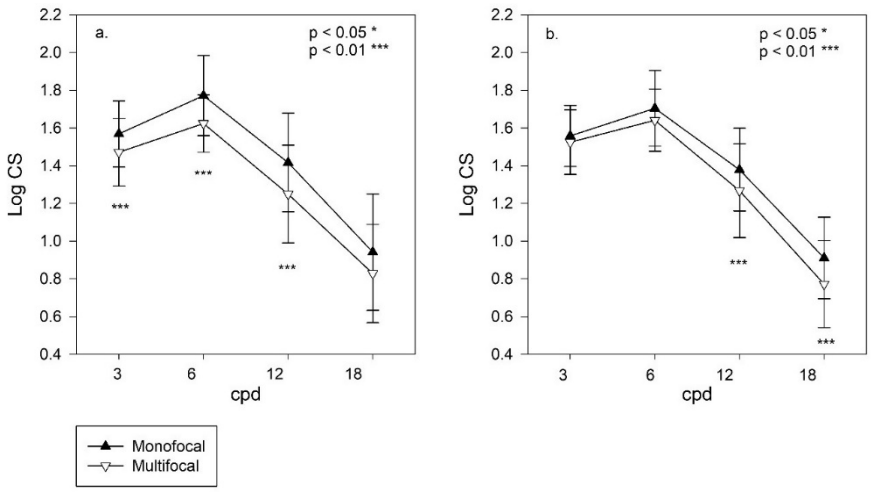


Figure 4.12: CSV-1000 Contrast Sensitivity. Error bars = standard deviation

a. Visit 1 CSV-1000 Contrast sensitivity
b. Visit 2 CSV-1000 Contrast sensitivity

Table 4.8: CSV-1000

	Monofocal	Multifocal	95% CI of the difference		*p*	Cohen's d
			Lower	Upper		
Visit 1						
3cpd	1.569 ± 0.175	1.471 ± 0.180	0.040	0.184	0.010	0.552
6cpd	1.771 ± 0.213	1.624 ± 0.152	0.086	0.236	<0.01	0.794
12cpd	1.417 ± 0.261	1.249 ± 0.260	0.079	0.291	<0.01	0.645
18cpd	0.942 ± 0.162	0.828 ± 0.261	0.000	0.239	0.061	0.523
Visit 2						
3cpd	1.558 ± 0.162	1.515 ± 0.172	-0.030	0.116	0.380	0.257
6cpd	1.704 ± 0.200	1.636 ± 0.161	-0.011	0.147	0.123	0.375
12cpd	1.379 ± 0.219	1.258 ± 0.249	0.019	0.224	0.034	0.516
18cpd	0.911 ± 0.216	0.765 ± 0.230	0.048	0.243	0.010	0.654

CI = confidence interval, cpd = cycles per degree
Data are mean ± standard deviation
Cohen d > 0.2 = small effect size, Cohen's d > 0.5 = medium effect size, Cohen's d > 0.8 = large effect size

4.6.7 Questionnaire

75% of the MIOL group were completely spectacle independent compared to 6.7% of the monofocal group at Visit1. At Visit 2, 66.7% and 4.7% respectively remained completely spectacle independent (Figure 4.13a, 4.13b).

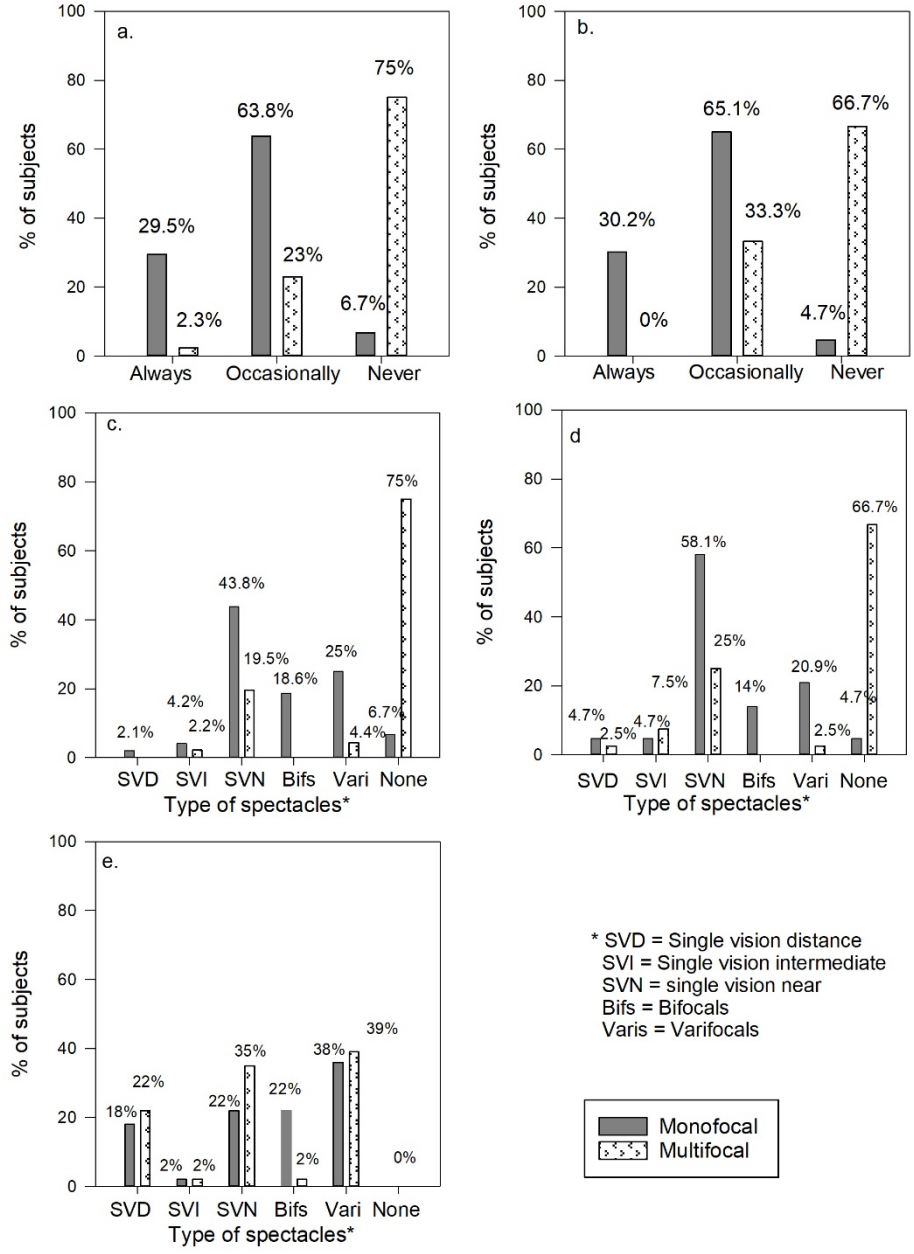


Figure 4.13: Spectacle Wear

a. Visit 1 Frequency of wear
b. Visit 2 Frequency of wear
c. Visit 1 Type of spectacles
d. Visit 2 Type of spectacles
e. Pre-Op spectacle wear

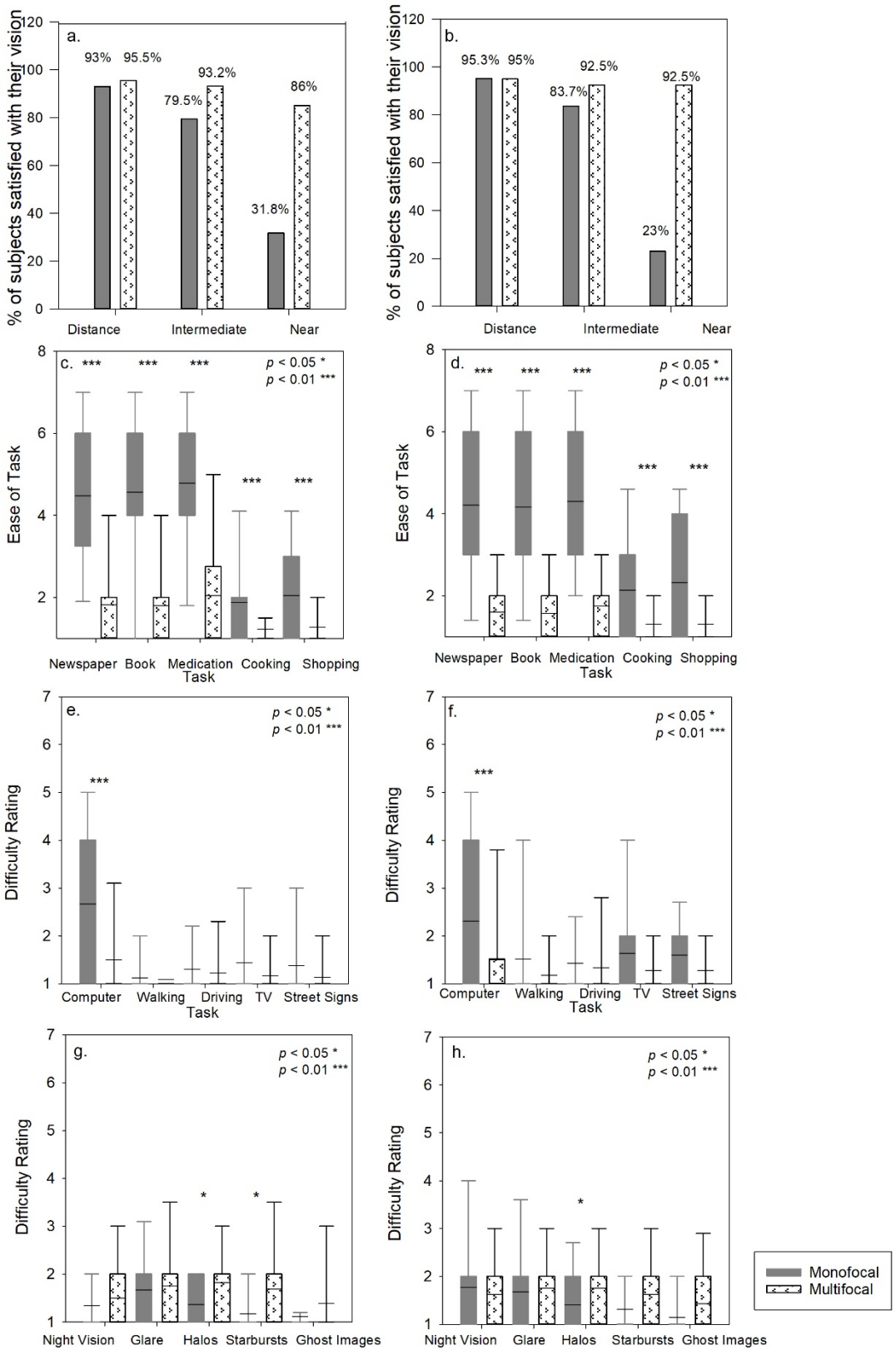


Figure 4.14: Quality of Vision. Error bars = standard deviation

a. Visit 1 Satisfaction
b. Visit 2 Satisfaction
c. Visit 1 Near Tasks
d. Visit 2 Near Tasks
e. Visit 1 Everyday Tasks
f. Visit 2 Everyday Tasks
g. Visit 1 Night Vision
h. Visit 2 Night Vision

The type of spectacles worn in both groups was different post-operatively compared to pre-operatively with fewer subjects using bifocals or varifocals. Single vision near spectacles (reading only) were the most common refractive correction in both groups. A small proportion of subjects used spectacles for distance; this finding was consistent with the satisfaction results. In addition 2.5% of the MIOL group used varifocal spectacles post-operatively due to patient preference for varifocals rather than single vision spectacles and not due to a need for full time correction. Difficulty scores were low for everday tasks such as driving and watching TV (**Figure 4.14**).

Overall satisfaction was high (> 90% of subjects) in both groups for distance tasks. Satisfaction was greater for the MIOL group at both intermediate and near (**Figure 4.14a, 4.14b**). Significant differences were found between groups for all near tasks (**Figure 4.14c, 4.14d**) and at both visits the monofocal group reported significantly more difficulty using a VDU screen (**Figure 4.14e, 4.14f**). However, satisfaction scores were similar for distance tasks such as driving and watching TV.

The MIOL group also had a significantly better NAVQ score (p<0.01), consistent with the greater spectacle independence achieved amongst participants in that group at both visits (**Figure 4.15).**

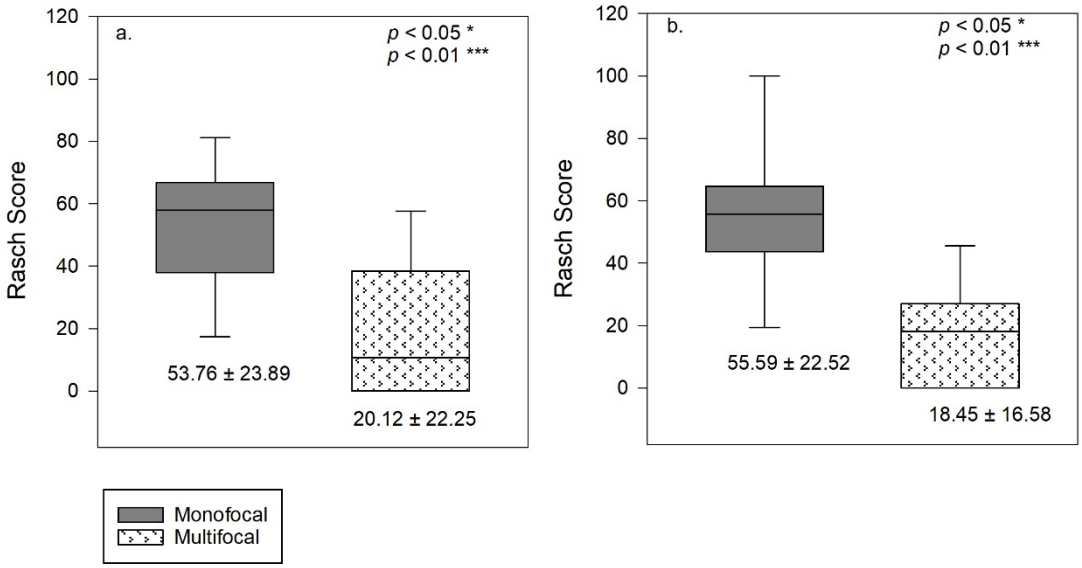


Figure 4.15: NAVQ Scores. Error bars = standard deviation

a. Visit 1 b. Visit 2

Subjects were asked to rate the difficulty invoked in general night vision, and with glare, halos, starburst and ghost images (**Figure 4.14g, 4.14h**). Significant difference between groups were only evident for halos at both visits; MIOL scores were higher but still categorised as low difficulty (between 1 and 3 for all subjects).

The Halo and Glare simulator (Eyeland Design Network, GmbH, Vreden, Germany) was used and subjects asked to adjust the settings in order to pictorially display halos/glare akin to those they observe at night. 77% of the MIOL group reported halos, compared to just 6% of the IOL group. Halo size and intensity was quantified using the simulator on a scale of 0 (no halo) to 100 (maximum). Results showed a significant difference in halo size (p <0.01) reported in the MIOL group at both V1 and V2 (**Figure 4.16**).

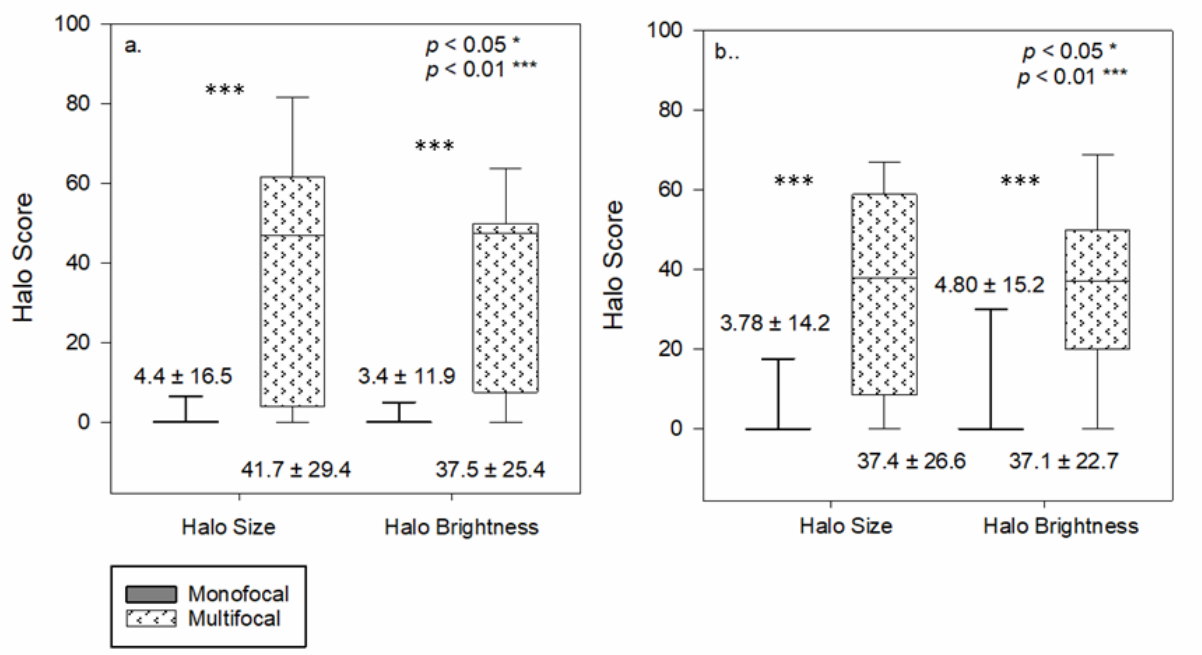


Figure 4.16: Simulator Scores**.** Error bars = standard deviation

a. Visit 1
b. Visit 2

The simulator also allows glare to be quantified, however this was <2.0 in both monofocal and multifocal groups and not statistically significant.

4.7 Discussion

The 2016 Cochrane review (de Silva et al., 2016) highlighted the need for the evaluation of MIOLs using a core set of standardised outcome measures and graded the current certainty of evidence for efficacy as very low to moderate. This RCT aimed to build on the existing evidence base by evaluating MIOLs using a comprehensive set of standard outcome measures.

In this study, participants were recruited from patients referred for cataract surgery under the UK NHS.

As such the subjects did not attend expecting MIOL implantation and were not motivated for achieving spectacle independence which may in fact have biased the results toward spectacle dependence. Conversely, most existing studies of this nature are non-randomised and hence prone to bias towards spectacle independence in addition to influencing IOL selection (Cochener et al., 2009). In addition, the mean age of the patients in this study represent the oldest population of all the IOL/MIOL RCTs and is the first, to our knowledge, where the patients had a mean age older than 75 years. As such, the results provide a generalised dataset for an older patient base.

When compared with monofocal IOLs, the present study demonstrated an improved unaided and best distance corrected near vision with the MIOL. Good uncorrected near vision is the primary motivation for MIOL implantation but assessing it requires a multifaceted approach. Previous studies have shown good near vision with bifocal IOLs and improved satisfaction with near tasks and spectacle independence (Cochener et al., 2009, Garcia-Bella et al., 2018, Ji et al., 2013). Our results are further supported by the defocus curve analysis, via both the traditional direct comparison method and through the area and range of focus metrics (Buckhurst et al., 2012b). Additionally, the Radner reading charts showed that a significantly smaller critical print size was achieved whilst maintaining maximum reading speed in the MIOL group. The subjective perception of near vision was also enhanced in the MIOL group as evident via the observations of the two questionnaires used in this study (QoV questionnaire (Law et al., 2014) and the previously validated NAVQ (Buckhurst et al., 2012a)); no differences in satisfaction scores were identified for the distance and intermediate vision.

It must be noted, in most studies, including this present study, an arbitrary reading distance of 40cm was used, this is likely to show optimum reading performance for an IOL that has an addition of +2.50D in the spectacle plane, however higher adds will have optimum acuity at a

shorter focal length. Therefore, it is possible that maximum UNVA and DCNVA has not been recorded due to this imposed working distance.

UDVA, CDVA and the direct comparison method of defocus curve analysis demonstrated no difference in vision at distance between the two lens types. However, the distance area of the defocus curve and contrast sensitivity measurements were lower in the MIOL group. This is consistent with the findings of other studies (Cillino et al., 2008, Harman et al., 2008, Ji et al., 2013, Kamlesh et al., 2001, Pedrotti et al., 2018, Wilkins et al., 2013, Zhao et al., 2010) and is an expected finding with any RCT comparing MIOLs with IOLs.

All MIOLS have a near focal point, which creates a myopic blur circle around the distance focal point; it is this blur that affects CS. The MIOL examined in the present study is designed to be distant dominant when viewing a distance object (provided a large pupil is present), this will reduce the intensity of the blur circle minimizing its impact on CS and preserving distance vision quality. By months 12-18, there were no significant differences in CS as measured on the Pelli-Robson and at all but the low spatial frequencies on the CSV-1000. Previous studies have shown that contrast sensitivity with MIOLs still falls within normal limits (Alfonso et al., 2007, Fernandez-Vega et al., 2007, Kaymak and Mester, 2007). Anton (Anton et al., 2014) included a monofocal control group and found that although contrast fell within the broad normal range, it was indeed reduced compared to monofocal control group. Despite this, patient satisfaction outcomes were not impacted. Given that there was no significant difference in distance visual acuity, and that the subjective satisfaction of distance vision was comparable, despite a reduction in contrast, it is probable that the lens design has minimized the impact of the blur circle to the point whereby it is no longer of clinical significance.

Subjects implanted with MIOLs reported halos at both visits according to both the questionnaire data and glare simulator. This is to be expected as these halos are created by

the defocus of the second focal point and are present with all MIOLs. The intensity of the halo is an important consideration with MIOL design. Theoretically distance dominant MIOL demonstrate lower halo intensities. The study MIOL incorporates a partially diffractive surface which is distance dominant with large pupil sizes and given that the perception of halos occurs mainly at night it is likely that the impact of halos on vision has been minimized: This may explain how, despite the presence of halos, overall satisfaction with distance vision was high (97%) and difficulty attributed to photopic phenomena was low.

Intermediate vision is relatively difficult to define and hence this study has used a variety of methods to assess visual function in this region. The intermediate area-of-focus metric defined by Buckhurst and colleagues (Buckhurst et al., 2012b) and used in this study evaluates vision quality between a defocus of -0.50 to -2.00D (corresponding to a working distance of approximately 0.50 to 2.00m). The intermediate area-of-focus results showed no significant difference between the MIOL and IOL; affirmed by the non-significant finding for intermediate vision using the ETDRS chart at 70cm.

The Direct comparison method of defocus curve analysis demonstrated an improved visual acuity with a -2.00D of optical defocus corresponding with a distance of 50cm. This is similar to the findings of Hayashi (Hayashi et al., 2009) who found that an MIOL of +3.00D addition vision provided similar acuities to a monofocal IOL at distances of 1.0 and 0.7m whilst better acuities at 0.5 and 0.3m. Hitherto, the only study to have examined the Bi-Flex MY MIOL was a non-control cohort study on 25 subjects (Garcia-Bella et al., 2018). Analogous to the present observations the investigators noted similar defocus curves with a peak in visual acuity at approximately -2.50D of defocus with a similar profile across the intermediate range. Comparability between the present study and this cohort study is limited as only mean defocus curve acuity values were reported and mean age of the cohort was over 10 years younger than

that of the present study. Subsequent to the results of this study, a revised version of this optic has been designed (the liberty MIOL) that distributes light to the intermediate zone.

Interestingly, in the present study the perception of quality of vision for computer use was superior amongst the MIOL group, suggesting that improved acuity at 0.5m is sufficient to notice an improvement in in vision for VDU use.67% of the MIOL group were found to be entirely spectacle independent, whilst the remaining 33% of patients only wore glasses occasionally. This is a lower level of spectacle independence than has been recorded in previous studies. (Baig et al., 2016, Cillino et al., 2008, Mendicute et al., 2016) Motivation for spectacle independence is likely to be an important factor in these disparate observations; given that in the present study, participants attended for cataract removal rather than for a specific refractive outcome. Individuals with a prior motivation to be spectacle independent are more likely to tolerate near and intermediate blur and hence comparability between studies can be limited.

Only 5% of the monofocal group was found to be spectacle independent with 30% requiring constant correction and the remaining 65% occasionally wearing spectacles. A disparity between the type of spectacles worn was evident between groups, with 35% of subjects implanted with monofocal IOLs wearing either bifocals or varifocals post-operatively when compared to just 3% of the MIOL group. It is important to note that overall satisfaction of distance vision was similar in both groups whilst satisfaction of near and intermediate vision was considerably greater in the MIOL group with 95% of subjects satisfied.

An earlier Cochrane review concluded that there were no consistent methods employed across studies to assess satisfaction and quality of vision, even studies which used the same questionnaire, had variable results. We utilized 2 different questionnaires, the wider ranging, but non-validated questionnaire (Law et al., 2014) and the near specific validated NAVQ

(Buckhurst et al., 2012a). Both methods found greater ease and satisfaction with near tasks in the multifocal group and correlation was significant between the questionnaires (R = 0.762, $p < 0.001$). Near Satisfaction was >85% in the multifocal group and may seem somewhat incongruous with the 67% spectacle independence in the same group. This highlights that spectacle independence/satisfaction are not necessarily co-dependent. This is further supported by the findings in the monofocal group. Despite only circa 5% being spectacle independent, >20% declared themselves to be satisfied with unaided near vision. It is also worth note that spectacle independence reduced slightly at V2 in the multifocal group, yet satisfaction scores increased. It would therefore be incorrect to assume that only subjects who are spectacle independent are truly satisfied. It is important to note that overall satisfaction of distance vision was similar in both groups with 95% of subjects satisfied.

At the time of study design, despite Cochrane Reviews calls for standardisation of methods there were no core outcome measures for MIOL studies, however, since completion of the study, a set of suggested outcomes have been published and largely support our study design (Evans et al., 2020). They specified that distance visual acuity near visual acuity, contrast sensitivity should always be measured with and without habitual spectacle correction using LogMAR chart and Pelli-Robson, in addition to spectacle independence and occurrence of dysphotopsia by way of a quality of life questionnaire (Evans et al., 2020). In contrast, to these suggestions, we used best distance correction in all subjects to ensure that any small uncorrected refractive errors did not have an impact on visual function. We concur that LogMAR tests should be used for distance and near acuity measures, however the choice of an arbitrary testing distance or patient preferred working distance can induce bias and limit the possibility of comparison with other literature. In addition, as intermediate vision is an important consideration for many, we believe it to be a necessary clinical metric in MIOL

studies. However, it remains relatively difficult to define and thus the choice of intermediate testing distance suffers the same potential bias as near assessment. The addition of defocus profiles to MIOL studies ensures a comprehensive view of the visual performance across a range of distances, and would mitigate the issues inherent with arbitrary testing distances and allow comparison between other MIOLs and studies. This study also highlights the importance of patient reported outcomes. Despite, the presence of significant halos compared to the monofocal group, the questionnaire was able to highlight that subjects did not feel these to be troublesome or adversely affect their satisfaction. The NAVQ questionnaire is useful in assessing satisfaction with near tasks but does not offer a global view on satisfaction. Evans (Evans et al., 2020) advocates for use of the VF-7 or VF-14 questionnaire, and while we appreciate the merits of this validated questionnaire in cataract outcomes, there is little attention to dysphotopsia. There is a single question regarding night driving, but it does not address the presence of halos and/or glare. Moreover, non-drivers will mark this "not applicable". However, this could be used in conjunction with the Halo simulator or an objective measure of halos to glean further information. In this study, we used our own non-validated instrument, however further work is required to establish a validated questionnaire truly suitable for MIOL analysis.

It was also evident from our results that in some measures there were clear differences between study visits, for example contrast sensitivity supporting the need for long term follow up in MIOL studies. Previous literature has proposed neuroadaptation as an active mechanism in MIOLs (Rosa et al., 2017a, Rosa et al., 2017b) and as such improvements in contrast and dysphotopsia can be expected at longer term visits. This has been supported in some studies but warrants further investigation (de Vries et al., 2008, Sood and Woodward, 2011).

4.8 Limitations

This study utilized a large number of measures and although VA is known to be highly repeatable (Raasch et al., 1998), there may have been a fatigue effect particularly with the 42 necessary measurements to complete monocular and binocular defocus testing. This study is also limited to photopic conditions only and thus, there has been no exploration of the effect of lower light conditions on the performance of the MIOL.

Pupil size was measured but the sample size insufficient to further group the subjects by pupil size to investigate the pupil dependency of the MIOL.

The age group for this study was perhaps older than in many studies and as such the number of active computer users and frequent night drivers reduced, so caution must be exerted in conclusions drawn in these areas, however other studies have neither specified that all subjects examined must fulfil these categories.

Another limitation is the use of the non-validated QoV questionnaire. Despite its use in a previous study, it has not been formally validated, nor undergone Rasch analysis. It was also developed with no patient involvement. This highlights the need for a validated MIOL questionnaire that could be used instead of or in conjunction with the NAVQ to assess patient reported outcomes that are not solely restricted to near visual function. No objective measurement of photic phenomena was undertaken, if the MIOL were to be compared to another MIOL, this would be a recommendation, in order to detect differences between the two.

4.9 Conclusion

Unaided near visual acuity is demonstrably improved with the Bi-Flex 677MY IOL with greater spectacle independence. Limitations in visual performance due to halos, glare and reduction in contrast were evident amongst the MIOL group, and although statistically significant, they do not appear to limit the subject's visual function nor their perception of vision and overall satisfaction. The rigorous methods employed ensure that main outcome measures were cross-validated by using more than one method of assessment. Visual acuity measures and defocus should be assessed for true comparison of range of clear vision achieved with IOLs. Patient reported outcomes should be assessed to accompany visual acuity findings, and not constrained to near performance alone, so use of a wider ranging questionnaire is advocated. Thus, the study concludes that the Bi-FLex 677MY multifocal IOL demonstrates efficacy for the correction of near and distance vision and is indicated when improved near vision/spectacle independence is required. The study also highlights that patient satisfaction is not solely influenced by spectacle independence in this group. However, spectacle independence may be the main indicator for satisfaction in a refractive lens exchange cohort as the patient's motivation for surgery and expectations will differ from a cataractous cohort. This study also suggests a robust protocol incorporating the main aspects of MIOL assessment. In order, to compare and contrast different multifocal IOLs, standardized methodology is required and we advocate the inclusion of visual acuity measures using LogMAR charts, defocus profiles, assessment of contrast sensitivity and spectacle independence along with a patient satisfaction questionnaire. In addition, reading performance can offer useful information. Patient satisfaction and visual performance with such lenses is multifactorial and thus studies which exclude relevant factors may give a misleading representation of a MIOL. Whereas following a robust protocol in future RCT and cohort studies would provide clinicians with meaningful

comparative data for MIOLs. In addition, differences in measures such as contrast sensitivity were seen at the second study visit, and support the theory of neuroadaptation in MIOLs and thus future studies should include a longer term (i.e 12 months) study visit.

Thus in summary, the primary findings of this study are:

- MIOLs provide improved near vision and spectacle independence compared to monofocal IOLs
- Patient satisfaction and spectacle independence was high with MIOLs
- Dysphotopsia was present but did not adversely affect satisfaction
- Our findings advocate the inclusion of the following measures in MIOL studies
    - Visual acuity (LogMAR)
    - Defocus profiles using detailed metrics
    - Contrast sensitivity
    - Spectacle independence
    - Patient reported outcomes/questionnaire
    - Assessment of dysphotopsia
- Long term follow up is required to assess the effects of neuroadaptation

Exploration of differing multifocal designs is required to assess the suggested protocol and study intervals further and establish its viability with alternative MIOL designs.

4.10 Supporting Publication

This chapter formed the basis for:

Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **Visual function and subjective perception of vision following bilateral implantation of monofocal and multifocal intraocular lenses: Randomised controlled trial.** *J Cataract Refract Surg*. 2020 Jul; 46(7): 1020 -1029. doi: 10.1097/j.jcrs.0000000000000210

Chapter Five

Visual function and patient satisfaction following bilateral implantation of trifocal and extended depth of focus intraocular lenses: A Prospective Cohort Study

OVERVIEW

Although bifocal IOL designs provide good distance and near acuity, they remain lacking in the intermediate zone. The advent of trifocal and extended depth of focus IOL designs addresses this shortcoming.

Using the methodology advocated in the previous chapter, this study aimed to compare a cohort of patients implanted with a trifocal to a cohort with extended depth of focus IOLs. In addition, previous comparisons have been short term only, thus this study also examined subjects one year post-operatively.

Intermediate area of focus was found to be greater in the extended depth of focus group, yet no significant differences were found in patient reported outcomes of intermediate tasks. Near vision was better in the trifocal group and spectacle independence greater. The longer term follow up highlighted changes to contrast sensitivity and dysphotopsia in line with neural adaptation

5.1 Introduction

In an era, where computer use is commonplace, intermediate vision has become increasingly important to patients considering surgery. Excellent distance and near visual acuity has been reported in bifocal IOLs as discussed in the Chapter 4, however intermediate vision is not significantly improved (Cochener et al., 2009, Kohnen et al., 2009, Madrid-Costa et al., 2013, Mojzis et al., 2014, Santhiago et al., 2011). There are various surgical options available to clinicians to improve intermediate vision; lower addition bifocals can be utilised, however this can compromise near visual acuity (Mastropasqua et al., 2015, Hayashi et al., 2009, Hayashi et al., 2015). Alternatively a mix and match approach, using a bifocal of different addition power in the contralateral eye (Mastropasqua et al., 2015) or a monovision approach (Chang et al., 2020, Finkelman et al., 2009, Labiris et al., 2015)with bifocal IOLs have both been shown to improve intermediate vision. Alternatives to bifocals and monofocals are now available, thus further increasing the intermediate options available.

5.1.1 Trifocals

Trifocal IOLs were introduced to provide an intermediate correction in addition to the near correction. Trifocals can be considered advantageous over bifocals as they improve intermediate vision and spectacle independence has also been reported to be higher (Cochener, 2016, Shen et al., 2017, Yang et al., 2018). Despite these advantages, trifocal IOLs have been linked to increased photopic phenomena in both *in vitro* (Carson et al., 2014, Madrid-Costa et al., 2013) and *in vivo* (Cochener, 2016, Jonker et al., 2015). However, there are contradictory findings from studies where either no difference was found (Alio et al., 2018a, Gatinel and Loicq, 2016) or indeed dysphotopsia was greater in bifocals (Rosen et al., 2016, Salerno et al., 2017).

5.1.2 Extended depth of focus

More recently, extended depth of focus (EDoF) IOLs have been marketed as an alternative to MIOLs and promise high quality intermediate acuity with minimal dysphotopsia (Cochener and Concerto Study, 2016). Comparative studies have shown unaided near vision to be inferior in EDoF IOLs compared to bifocal and trifocals but intermediate and distance vision to be similar (Cochener et al., 2018, Mencucci et al., 2018, Monaco et al., 2017, Pedrotti et al., 2018, Webers et al., 2020).

Moreover, manufacturer guidance suggests that extending the depth of focus is unlikely to produce the halos and glare that we expect in MIOLs using simultaneous perception (Cochener and Concerto Study, 2016), the literature, however, is equivocal on the validity of this guidance, as dysphotopic symptoms are still reported in some studies (Escandon-Garcia et al., 2018, Liu et al., 2019). The definition of an EDoF is relatively inclusive and hence there is a diverse assortment of optical principles for which these lenses are based including; diffractive optics, refractive, small aperture designs, bioanalogic hydrogels, and asphericity as discussed in Chapter 1.13 (Cochener and Concerto Study, 2016, Kohnen and Suryakumar, 2020, Sudhir et al., 2019)'.

5.1.3 Current Literature

Many cohort studies have been published investigating both trifocal and EDoF IOLs. The bilateral comparative studies between EDoF and MIOLs are listed in Table 5.1, however our literature search revealed there are only five which directly compare clinical outcomes of the AT LISA 839MP trifocal MIOL and the Tecnis Symfony EDoF IOL (Bohm et al., 2019, Hamid, 2016, Mencucci et al., 2018, Palomino-Bautista et al., 2020, Webers et al., 2020). There is considerable variation in the methodology used within these studies.

Of these studies, follow up interval was only short-term (3 months) in both (Bohm et al., 2019, Mencucci et al., 2018, Webers et al., 2020) and 6 months in Hamid's study (Hamid, 2016). One study also targeted micro-monovision in the EDoF group in order to improve near performance (Webers et al., 2020). In the final study, only defocus and aberometry was assessed (Palomino-Bautista et al., 2020). There was variation in the results of the studies, Hamid (Hamid, 2016) found that distance and intermediate vision were better in the EDoF group, whereas Bohm (Bohm et al., 2019) found distance and intermediate to be comparable between the EDoF and Trifocal groups.

Table 5.1: Summary of comparative studies

Author	IOLs	Description	Subjects	Eye	Randomised	Visits	Tests
Hamid 2016	AT LISA 839MP Tecnis Symfony Finevision	Trifocal EDoF Trifocal	50 50 50	Bilateral	No	2/12, 3/12 6/12	UDVA, CDVA, DCIVA, DCNVA PelliRobson Defocus Satisfaction questionnaire
Monaco 2017	Panoptix Tecnis Symfony SN60WF	Modified quadrifocal EDoF Monofocal	20 20 20	Bilateral	Yes	4/12	UDVA, CDVA, DCIVA, DCNVA Defocus Aberometry Questionnaire
Cochener 2018	Finevision Panoptix Tecnis Symfony	Trifocal Modified quadrifocal EDoF	20 20 20	Bilateral	Yes	6/12	UDVA, CDVA, DCIVA, DCNVA MTF and Aberometry Questionnaire
Escandon-Garcia 2018	Finevision PanOptix Symfony	Trifocal Modified quadrifocal EDoF	23 7 15	Bilateral	No	?	UDVA, CDVA, DCIVA, DCNVA FACT Defocus +1.00 to -3.00
Mencucci 2018	Tecnis Symfony AT LISA 839MP Panoptix	EDoF Trifocal Modified quadrafocal	20 20 20	Bilateral	No	3/12	UDVA, UNVA CDVA, DCIVA, DCNVA MNRead Questionnaire
Pedrotti 2018	Tecnis Monofocal Tecnis Symfony ReStor +2.50 ReStor +3.00	Monofocal EDoF Bifocal Bifocal	30 55 50 50	Bilateral	No	6/12	UDVA, CDVA, UIVA, CIVA, DCIVA,UNVA, CNVA, DCNVA CSV-1000 OQAS NEI RQ

OQAS = Optical Quality Assessment System, NEIRQL = National Eye Institute Refractive Error Quality of Life, VQOL = vision related quality of life, VF-14 = visual function questionnaire, FACT = functional acuity contrast test, MTF= modulation transfer function

Table 5.1b Summary of Comparative Studies							
Ruiz-Mesa 2018	PanOptix Tecnis Symfony	Modified Quadrifocal EDoF	20 14	Bilateral	No	?	UDVA, CDVA, DCIVA, DCNVA FACT Defocus +1.00 to -4.00 Halometry and Aberrometry
Bohm 2019	AT LISA 839MP Tecnis Symfony Panoptix Mplus	Trifocal EDoF Modified quadrifocal Bifocal	27 26 27 25	Bilateral	No	3/12	UDVA, CDVA UIVA, DCIVA UNVA, DCNA Defocus +1.50 to -4.00 Questionnaire
Singh 2019	Finevision Tecnis Symfony	Trifocal EDoF	40 40	Bilateral	No	6/12	UDVA, CDVA, DCIVA, DCNVA Quality of vision questionnaire
Palomina-Bautista 2020	Tecnis Symfony MiniWell AT LISA 839MP FineVision Tecnis ZMB Tecnis ZLB	EDoF EDoF Trifocal Trifocal Bifocal Bifocal	20 10 10 20 20 20	Bilateral	No	1/12	Defocus +1.00 to -1.00 Aberrometry
Webers 2020	Tecnis Symfony AT LISA 839MP	EDoF Trifocal	15 15	Bilateral	No	1/12 and 3/12	UDVA, CDVA, UIVA, uNVA Defocus +2.00 to -4.00 CSV-1000 Salzburg reading VQOL and VF-14 questionnaires

OQAS = Optical Quality Assessment System, NEIRQL = National Eye Institute Refractive Error Quality of Life, VQOL = vision related quality of life, VF-14 = visual function questionnaire, FACT = functional acuity contrast test, MTF= modulation transfer function

Therefore, the aims of this study are:

- Use a robust methodology for comparison of an EDoF and a Trifocal IOL
- Comprehensive assessment of visual function and the subjective perception of vision
- To provide long term follow up

5.2 Study Design

This study was a prospective cohort study. The protocol adheres to the tenets of the Declaration of Helsinki and ethical approval from the University of Plymouth ethics board was obtained prior to commencement of the study (Ref 13/14-271 and 13/14-239)(Appendix 1). Written consent was obtained from all subjects. No modification to the protocol or outcome measures were made during the study.

5.2.1 Patient Selection

Ninety-five subjects were recruited from routine cataract and refractive lens exchange clinics at the BMI Southend Hospital, UK on a consecutive-if-eligible basis based on the inclusion/exclusion criteria detailed in Table 5.2. In addition, all subjects had a comprehensive slit lamp examination and dilated fundus check. If there was any suspicion of macular pathology then an OCT was also performed. Subjects with a poor ocular surface, that was likely to contribute to a reduction in visual acuity, were advised to commence ocular lubricants and were excluded from this study.

Table 5.2: Inclusion/Exclusion Criteria	
Inclusion	**Exclusion**
Age 40 – 75 years	Subjects with glaucoma
Participants requiring bilateral primary IOL implantation	Previous intraocular and/or corneal surgery
Participants with a potential corrected visual acuity of 0.3 LogMAR or better on clinical assessment in both eyes	Subjects using a systemic medication that is known to cause ocular side effects
Subjects with clear intraocular media and normal anterior segment other than cataract	Subjects with macular or retinal pathology
< 1.00D of preoperative corneal astigmatism	Subjects who could not make an informed consent

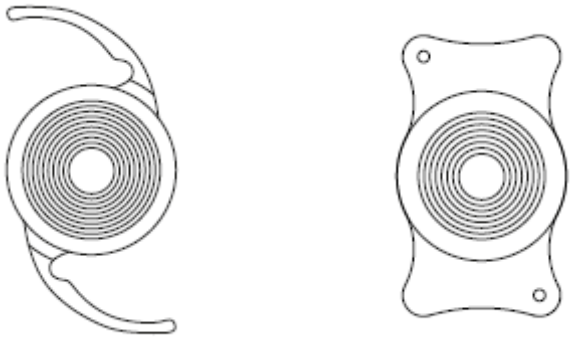
5.2.2 IOL Selection

Subjects were not randomised and the IOL choice was at the discretion of the surgeon and the patient following pre-operative assessment and discussion. Pre-operative assessment included detailed discussion of subject's lifestyle, occupation and preferences for reading distance and computer use. Subjects were introduced to the concept of halos and glare, by using the Eyeland Simulator (Eyeland Design Network, GmbH, Vreden, Germany) to illustrate. Written information describing the options available were given to all subjects to take home and consider. Final decision on IOL choice was made at a second pre-operative visit.

5.2.3 Intraocular Lenses

Two IOLs were included in this study, the Tecnis Symfony EDoF IOL (20 subjects) and the AT LISA 839MP Trifocal IOL (75 subjects) (**Table 5.2**). The Tecnis Symfony (Johnson & Johnson) has a diffractive pattern and also an achromatic posterior surface to compensate for the chromatic aberration of the cornea (Zhao and Mainster, 2007). The AT LISA 839 MP (Carl

Zeiss Meditec) is a trifocal IOL with a +3.33D near addition and a +1.66D intermediate addition.



a. **b.**

Figure 5.1: a. Tecnis Symfony EDoF IOL b. AT LISA 839MP Trifocal IOL

Table 5.3: MIOL Characteristics

	Tecnis Symfony	AT LISA Trifocal 839MP
Material	Hydrophobic acrylate	Hydrophillic acrylic (25%) with hydrophobic surface
Design	Diffractive 4.9mm zone Achromatic posterior surface Pupil independent	Diffractive Bifocal (4.34mm to 6.00mm) Diffractive trifocal (<4.34mm) Pupil independent
Addition	+1.75D intermediate	+3.33D Near +1.66D Intermediate
Spherical Aberration	-0.27µm	-0.18µm
Refractive Index	1.47	1.46
Range	5D to 34D (0.50D steps)	0D to 32D (0.50D steps)
Optic Diameter	6mm	6mm
Overall Length	13mm	11mm
Haptic	C-loop	plate haptic design

5.3 Surgical Technique

All surgeries were performed by one of two experienced consultant ophthalmic surgeons (RA and HK) using small incision phacoemulsification. The same surgeon implanted both lenses for an individual subject.

5.3.1 Pre-Surgery Medication

Topical anaesthesia was achieved by administration of Minims®Proxymetacaine hydrochloride 0.5% (Bausch & Lomb) eye drops prior to and during surgery. The mydriatic agents, Minims®Tropicamide 1% (Bausch & Lomb) and Minims® Phenylephrine 2.5% (Bausch & Lomb) were used to achieve adequate pupil dilation. Finally, 250mg Acetazolomide was given orally as routine practice.

5.3.2 Surgical Technique

Small incision phacoemulsification with a 2.2mm clear corneal incision as detailed in Section 1.3.2 was performed. The OVD used was Hydroxypropyl Methylcellulose (HPMC) and where possible the incision was located according to the steepest corneal meridian. Antibiotics (1% cefuroxime) were given intracamerally in all subjects prior to completion of surgery.

5.3.3 Post-Surgical Medication and Advice

For a period of twenty four days post-operatively, all subjects were instructed to use Tobradex 3mg/ml/1mg/ml (Novartis) four times daily. Standard post-operative advice was provided verbally and as an information leaflet.

5.3.4 Post-Operative Visit

One week after first eye surgery, subjects were asked to attend routine post-operative check with the consultant, if no complications were identified then the subject was given a surgical date for the second eye within 3 weeks. Following second eye surgery the subject was asked to return for follow up 4 weeks post-surgery.

5.4 Method

This study utilised the same protocol as described previously in Chapter 4 and a brief summary of outcome measures can be found in Table 5.4 below.

Table 5.4: Clinical Measures

	Outcome Measure	Method
Primary Outcome Measures	Subjective Refraction	6m LogMAR computerised chart
	Unaided Distance Vision (UDVA) and best corrected distance VA (CDVA)	6m LogMAR computerised chart Monocular and Binocular
	Unaided near vision (UNVA) and distance corrected near VA (DCNVA)	40cm ETDRS Near Acuity Chart Monocular and Binocular
	Distance corrected intermediate VA (DCIVA)	70cm ETDRS Near Acuity Chart Monocular and Binocular
	Defocus Curves (+1.50D to -5.00D in 0.50D steps)	6m LogMAR computerised Chart Binocular
Secondary Outcome Measures	Contrast Sensitivity	Pelli-Robson 6m LogMAR computerised chart Monocular and binocular CSV-1000 2m chart Binocular
	Reading Speed	40cm Radner Reading Chart Binocular
	Quality of Vision	Subjective questionnaire
	NAVQ	Subjective questionnaire
	Halos and Glare	Eyeland Designs Halo and Glare Simulator

Subjects were reviewed at two study visits, Visit 1 (3-6 months post-operatively) and Visit 2 (12-18 months post-operatively). All measures were performed in photopic lighting conditions of illuminance 120 cd/m^2 and luminance 95 lux. All post-operative visits were conducted by the same clinician (EL) who was independent of the IOL selection process but not masked to the IOL type implanted.

5.5 Statistical Analysis

Statistical analysis was performed using SPSS software, version 24 (SPSS Inc, IBM, Armonk, NY, USA). All data were tested for normality. In all instances a *p* value of <0.05 was considered statistically significant. Due to unequal sample sizes, Levene's test for equality of variances was performed in each instance and appropriate tests used thereafter. In addition, Hedge's g was calculated to demonstrate effect size.

5.5.1 Assumption of normality

The Shapiro- Wilks test was used to test normality and parametric testing or non-parametric testing where indicated was used thereafter.

5.5.2 Comparison of eyes

A repeated measures ANOVA was used to establish similarity between right and left eyes in both IOL groups (Ray and O'Day, 1985). No significant differences were found, thus only right eye data is presented for monocular measures.

5.5.3 Demographics

Independent *t* tests were used to check for similarities in the patient demographics

5.5.4 Visual acuity and contrast sensitivity

One-way and two-way ANOVA tests were used to compare differences between IOL groups for VA and contrast sensitivity measures and between monocular and binocular results within each group. Where differences were found, further pairwise *post hoc* analysis was performed.

5.5.5 Refraction

Manifest spherical equivalent was calculated (**Equation 4.1**). In order to accurately compare astigmatic effects, the Thibos method was used, and cylindrical correction was defined in terms of J_0 and J_{45} (Thibos et al., 1997)(**Equation 4.2 and 4.3**).

5.5.6 Defocus

As in **Chapter 4**, three methods were used to describe defocus curves; direct comparison, area of focus and range of focus. All data was corrected for spectacle magnification (**Equation 2.2**). Direct comparison of defocus was done by repeated measures ANOVA, with *post hoc* analysis. Following the methods discussed in **Chapter 2**, fitting a cubic spline curve was fitted (MATLAB R2017b, The Mathworks Inc, Matick, MA, USA) allowing, Area of Focus and Range of focus metrics to be calculated. (Buckhurst et al., 2012b).

5.5.7 Radner Reading

The Radner reading data was fitted with a non-linear regression curve (exponential rise to a maximum) following calculation of reading speed using SigmaPlot Version 13.0 (Systat Software Inc, San Jose, CA, USA)(**Equation 4.4**). Maximum reading speed (MRS) was defined as the asymptote of this curve and critical print size (CPS) was calculated as the value for *x* (print size) when the reading speed was 95% of the MRS. Radner acuity was defined as the small print size read. The data was analysed using a repeated measures ANOVA.

5.5.8 Questionnaire

Conversion of the NAVQ results to a Rasch score allowed significance to be determined with a Wilcoxon rank-sum test within groups and Mann-Whitney U test between groups. The same methods were applied to Quality of vision questionnaire also.

5.5.9 Halo and Glare Simulator

The scores for each individual were collated and the size and intensity scores were compared between groups using independent *t* tests and within groups using the Students *t* test.

5.6 Results

Ninety-Five subjects were assessed, 20 subjects had bilateral implantation of the EDoF IOL, and 75 subjects were bilaterally implanted with the Trifocal IOL.

5.6.1 Patient Demographics

Of the subjects recruited to the study, 75% presented initially for refractive lens exchange and had good pre-operative visual acuity > 0.20 LogMAR. The remaining subject presented due to symptomatic lens opacities in either one or both eyes. The majority of subjects (59%) were hyperopic (> +0.50 MSE) prior to surgery. There were no surgical complications. No significant differences between subject groups were observed pre-operatively (Table 5.5).

In each measure homogeneity was established with the exception of age where variances were not equal $F_{1,4} = 10.5$, $p < 0.01$ and this was accounted for. No significant differences were found between groups in any pre-operative measures (Table 5.5).

Table 5.5: Patient Demographics

	EDoF	Trifocal	*p*
Number of subjects	20	75	
Male/Female	35% / 65 %	23% / 67%	
Mean age (yrs)	63.5 ± 12.6	61.2 ± 7.9	0.78
Range (yrs)	53-74 years	51 -75 years	
Pre-Op Refractive Error (DS)			
Spherical Equivalent Range	-8.00 to +1.83	-9.13 to +7.00	0.60
MSE	-0.70 ± 3.05	-0.23 ± 3.51	
Pre-Op visual acuity (logMAR)			
RE CDVA	0.17 ± 0.14	0.13 ± 0.21	0.68
IOL Power (D)			
Range	10 to 25	8 to 30	
Mean	20.4 ± 3.0	20.1 ± 4.8	0.72

Data are mean ± Standard deviation ; RE: right eye; CDVA = Corrected distance visual acuity, IOL = Intraocular lens ,MSE = Manifest spherical equivalent

5.6.2 Refraction

There was a significant improvement to MSE post-operatively in both groups ($p<0.01$). When assessing the post-operative refraction no significant difference was identified between groups nor were there any significant differences between visits 1 and 2 (Table 5.6).

Table 5.6: Refraction			
Spherical Equivalent	**EDoF**	**Trifocal**	***p***
Visit 1			
Right Eye MSE	-0.09 ± 0.52	0.02 ± 0.25	0.79
J0	0.04 ± 0.43	0.03 ± 0.41	0.83
J45	0.00 ± 0.09	0.01 ± 0.13	0.23
Visit 2			
Right Eye MSE	-0.01 ± 0.40	0.04 ± 0.29	0.85
J0	0.13 ± 0.49	0.01 ± 0.39	0.39
J45	0.04 ± 0.11	0.03 ± 0.14	0.90
MSE = manifest spherical equivalent, J0 = cylindrical effect at 180°, J45 = cylindrical effect at 45° Data are mean ± standard deviation Units = Dioptres			

5.6.3 Visual Acuity

5.6.3.1 Visual Acuity within groups

Repeated measures ANOVA compared VA for right eyes, left eyes and binocular data. In the trifocal group $F_{2,15}$ = 887.20, $p < 0.01$ and *post hoc* analysis confirmed no differences between right and left eye data (p = 0.80) thus only right eye data is used from this point onwards. Similar results were found in the EDoF group $F_{2,15}$ =171.13, $p<0.01$, post *hoc* analysis confirmed no differences between right and left eyes (p= 0.64).

Within each IOL group, no significant differences were identified for any VA measures between Visits 1 and 2.

5.6.3.2 Visual Acuity between groups

There were no significant differences for UDVA, CDVA or DCIVA (**Table 5.7, Figure 5.2**).

Table 5.7: Visual Acuity Results						
	EDoF	Trifocal	95% CI of the difference		*p*	Hedge's g
			Lower	Upper		
Visit 1Monocular						
UDVA	0.09 ± 0.10	0.08 ± 0.09	-0.04	0.06	0.75	0.10
UNVA	0.35 ± 0.15	0.24 ± 0.11	0.05	0.17	<0.01***	0.84
CDVA	0.00 ± 0.07	0.02 ± 0.05	0.00	0.04	0.37	0.32
DCIVA	0.15 ± 0.17	0.21 ± 0.11	0.00	0.12	0.28	0.41
DCNVA	0.31 ± 0.19	0.20 ± 0.11	0.07	0.19	<0.01***	0.95
Visit 1 Binocular						
UDVA	0.02 ± 0.06	0.03 ± 0.06	-0.02	0.04	0.51	0.17
UNVA	0.33 ± 0.16	0.21 ± 0.10	0.06	0.18	<0.01***	0.90
CDVA	-0.02 ± 0.08	0.00 ± 0.05	0.00	0.04	0.69	0.30
DCIVA	0.14 ± 0.16	0.20 ± 0.11	0.00	0.12	0.06	0.43
DCNVA	0.31 ± 0.16	0.18 ± 0.10	0.07	0.19	<0.01***	0.97
Visit 2Monocular						
UDVA	0.05 ± 0.07	0.07 ± 0.09	-0.02	0.06	0.67	0.23
UNVA	0.31 ± 0.06	0.19 ± 0.08	0.08	0.16	<0.01***	1.57
CDVA	-0.02 ± 0.05	0.00 ± 0.06	0.00	0.05	0.23	0.34
DCIVA	0.15 ± 0.10	0.18 ± 0.08	-0.01	0.07	0.19	0.69
DCNVA	0.29 ± 0.06	0.20 ± 0.25	-0.02	0.20	0.01*	0.40
Visit 2 Binocular						
UDVA	-0.01 ± 0.05	0.03 ± 0.07	0.01	0.07	0.10	0.30
UNVA	0.28 ± 0.07	0.17 ± 0.08	0.07	0.15	<0.01***	1.41
CDVA	-0.04 ± 0.05	-0.02 ± 0.06	-0.01	0.05	0.24	0.34
DCIVA	0.12 ± 0.11	0.18 ± 0.08	0.02	0.10	0.07	0.68
DCNVA	0.29 ± 0.07	0.15 ± 0.07	0.11	0.18	<0.01***	2.00

CDVA = corrected distance visual acuity, CI = confidence interval, DCIVA = distance corrected intermediate visual acuity, DCNVA = distance corrected near visual acuity, UDVA = unaided distance visual acuity, UNVA = unaided near visual acuity acuity

Data are mean ± standard deviation

Hedge's g > 0.2 = small effect size, Hedge's g > 0.5 = medium effect size, Hedge's g > 0.8 = large effect size

*<0.05, ***<0.01

5.6.3.3 Distance Visual Acuity

Within the EDoF group, the UDVA was significantly better binocularly than monocularly at both Visit 1 ($p < 0.01$) and Visit 2 ($p = 0.02$), in comparison, there was no significant differences between the monocular and binocular UDVA results with the trifocal IOL. There were no significant differences between groups for CDVA monocularly or binocularly.

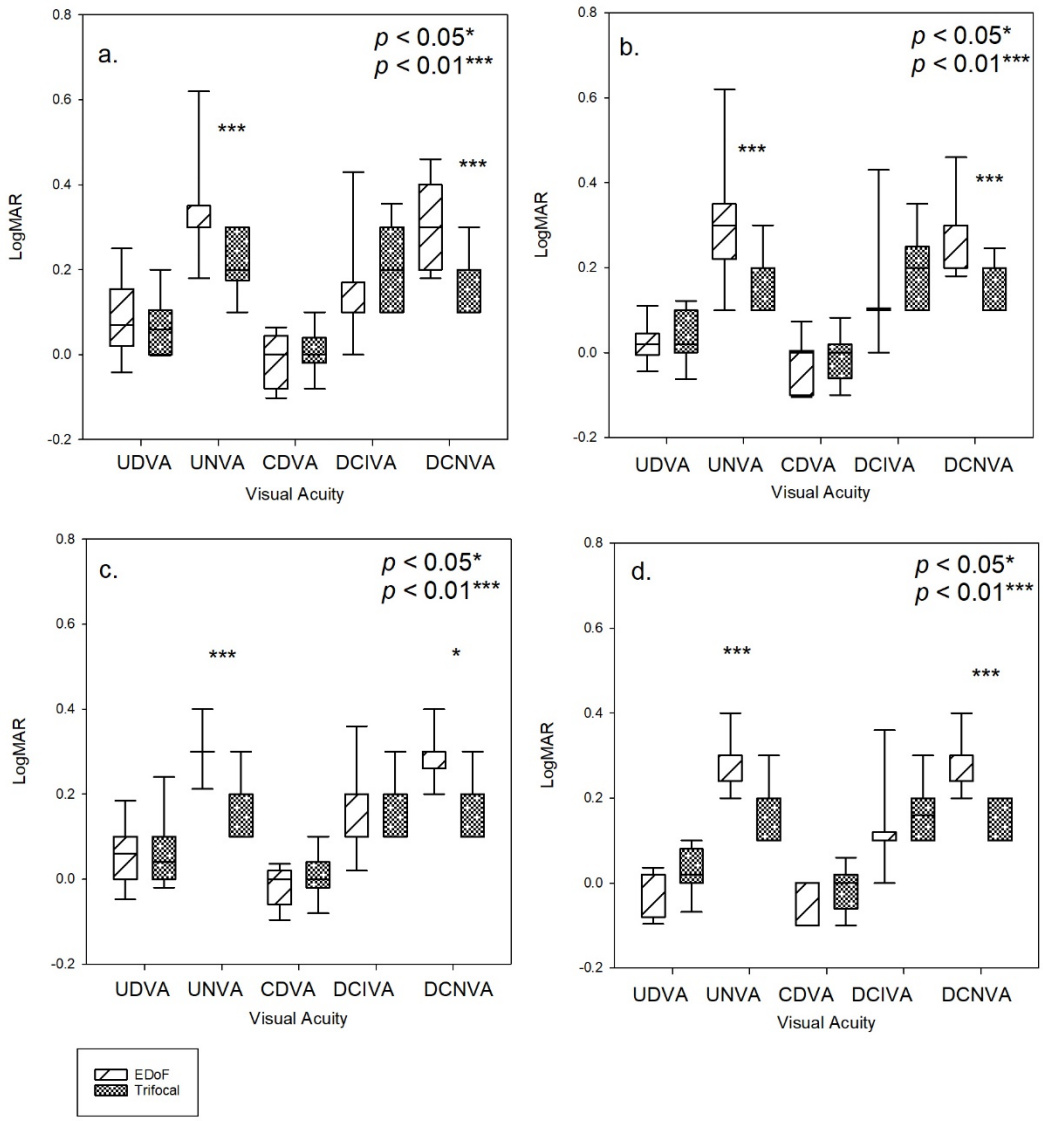


Figure 5.2: Visual Acuity. Error bars = standard deviation

a. V1 Monocular Visual Acuity
b. V1 Binocular Visual Acuity
c. V2 Monocular Visual Acuity
d. V2 Binocular Visual Acuity

5.6.3.4 Intermediate and Near Visual Acuity

Significant differences were found between groups for near vision. There were significant differences monocular for UNVA (p <0.01) and DCNVA (p = <0.01) and binocularly UNVA (p < 0.01) and DCNVA (p <0.01) at V1. At Visit 2, significant differences were also found between

groups for monocular UNVA, binocular UNVA and DCNVA ($p < 0.01$) and for monocular DCNVA ($p = 0.01$).

The differences between groups for intermediate visual acuity (DCIVA) measured at 70cm were not statistically significant, yet medium effect sizes (Hedge's $g > 0.3$) were seen at both visits. *Post hoc* power analysis, found power of 0.40 at Visit 1 and 0.78 at Visit 2. Both visits suggest inadequate power to rule out a Type II error.

5.6.4 Defocus

Repeated measures ANOVA with post hoc analysis found no differences between visits in the trifocal group ($F_{1, 13} = 0.392$, $p = 0.535$) or the EDoF group ($F_{1, 13} = 0.166$, $p = 0.687$. Direct comparison of binocular defocus curves with a one way ANOVA and pairwise comparisons found the trifocal group to have statistically better visual acuity from defocus -2.50 to -5.00 at both visits. The EDoF group had better VA at -0.50 defocus (working distance of 2m) ($p = 0.03$) at Visit 1 only and at -1.50 defocus (working distance of 67cm) at Visit 2 ($p = 0.02$), otherwise there were no significant differences through the distance and intermediate range (0.5 to -2.00D of defocus) (**Figure 5.3**).

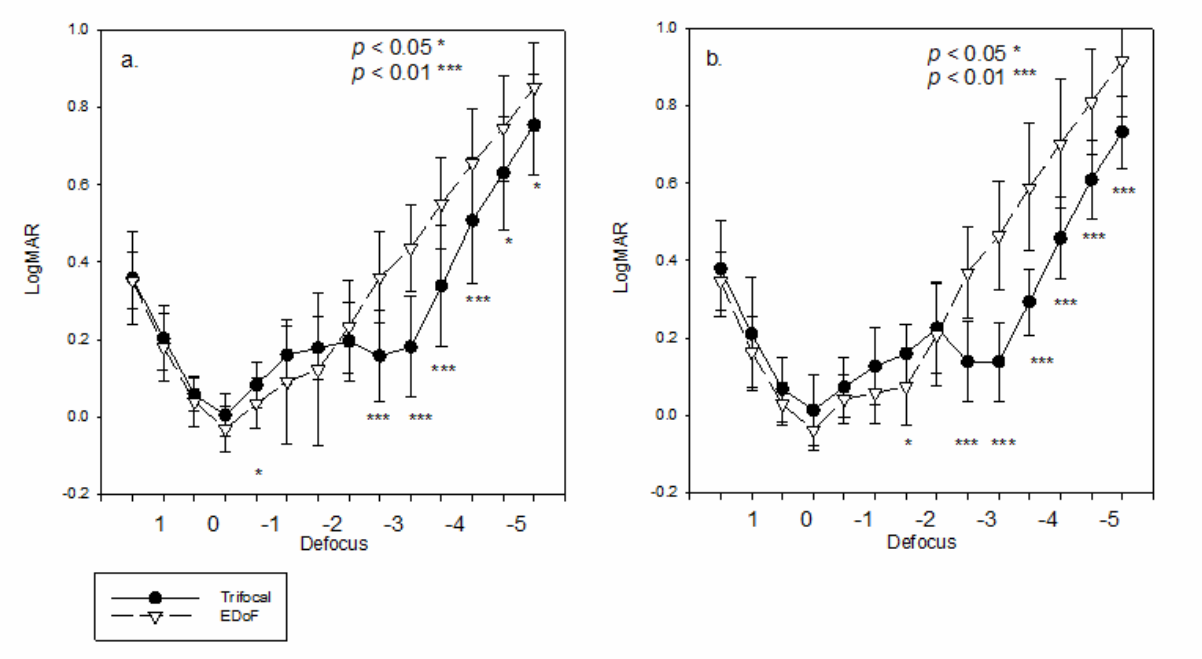


Figure 5.3: Defocus profiles. Error bars = standard deviation

a. Visit 1 Defocus
b. Visit 2 Defocus

The area of focus method of defocus analysis was performed (**Figure 5.4, Table 5.8**), no significant differences were found in the distance region (0.5 to -0.5D) at V1, but the distance area in the EDoF groups was found to be significantly larger at V2 compared to the trifocal (p = 0.02).

Table 5.8: Area of Focus

Visit 1		EDoF	Trifocal	p	Hedge's g
Area of Focus	Distance	0.31 ± 0.05	0.27 ± 0.04	0.07	0.60
	Intermediate	0.31 ± 0.12	0.22 ± 0.08	0.01*	0.88
	Near	0.03 ± 0.03	0.21 ± 0.10	<0.01***	2.68
Range of Focus	Actual	3.48 ± 0.65	4.49 ± 1.10	<0.01***	1.08
Visit 2					
Area of Focus	Distance	0.32 ± 0.05	0.28 ± 0.04	0.02*	1.20
	Intermediate	0.32 ± 0.11	0.23 ± 0.08	0.01*	1.17
	Near	0.02 ± 0.03	0.23 ± 0.08	<0.01***	2.04
Range of Focus	Actual	3.50 ± 0.61	4.27 ± 1.92	<0.01***	0.58

Data = Mean ± standard deviation
Distance = 0.50D to -0.50D defocus, Intermediate = -0.50D to -2.00D defocus and Near = -2.00D to -4.00D defocus
Unit for Area = Area for Range = diopters (D)

The EDoF had a significantly larger intermediate area (-0.5 to -2.00)(p = 0.01) at both visits and the Trifocal performed better in the near range (-2.00 to -4.00D)(p<0.01) at both visits.

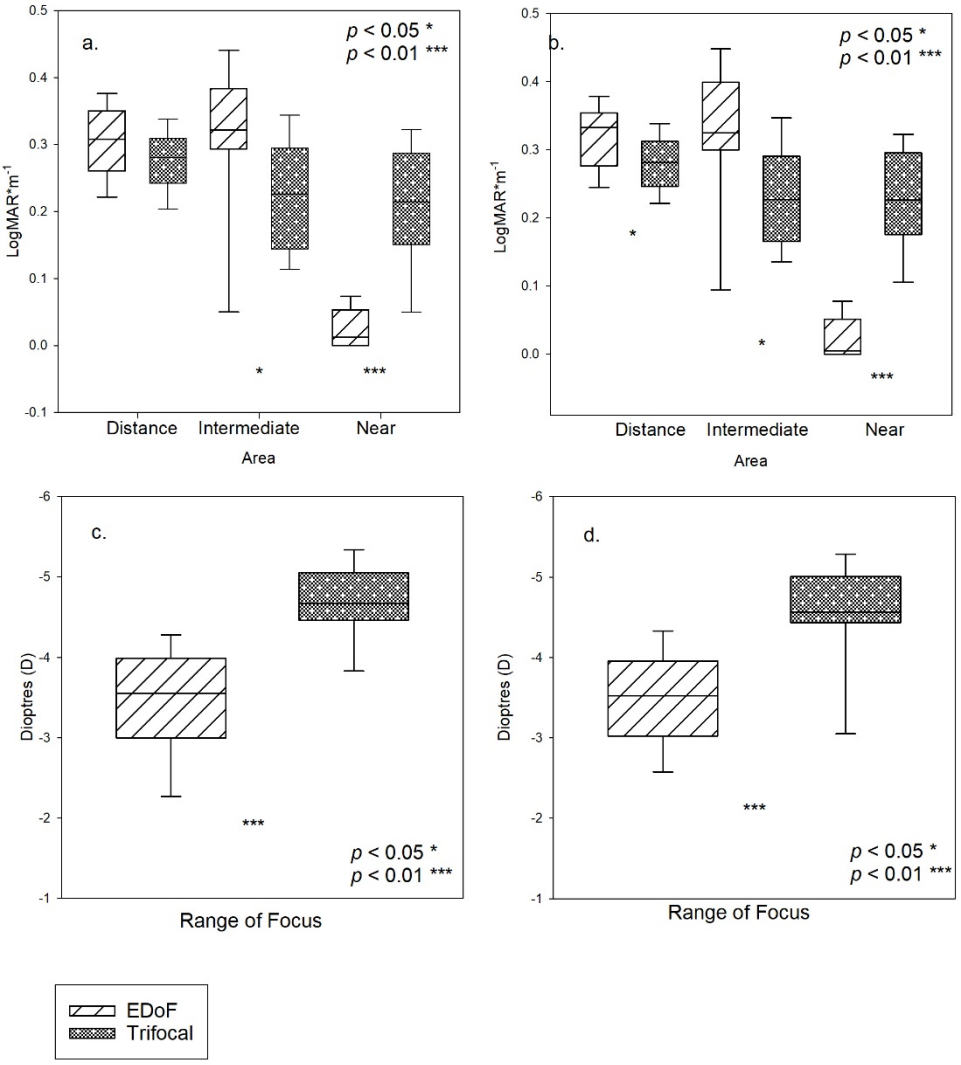


Figure 5.4: Defocus metrics. Error bars = standard deviation

a. Area of Focus V1
b. Area of Focus V2
c. Range of Focus V1
d Range of Focus V2

Assessment of absolute range of focus metrics with a cut off value of 0.30 LogMAR acuity highlighted differences between groups. As neither the EDoF nor Trifocal group had VA below 0.30LogMAR throughout the intermediate defocus range the results for actual range of focus and total range of focus were identical. There was a significantly larger range of focus with the trifocal group at both visits (p <0.01) (Figure 5.4b, Table 5.8).

5.6.5 Radner

There were no significant differences for CPS, Radner acuity or reading speed between visits in either of the groups. However, there were significant differences in both Radner acuity and critical print size between groups with the trifocal performing better in both measures at V1 and V2. There was also a significantly faster maximum reading speed in the trifocal group (Table 5.9, Figure 5.5).

Table 5.9: Radner Reading Assessment

	EDoF	Trifocal	p	Hedge's g
Radner Acuity	0.28 ± 0.10	0.13 ± 0.08	<0.01***	1.77
CPS 95%	0.69 ± 0.26	0.48 ± 0.23	0.03*	0.88
Maximum Reading Speed	150.50 ± 27.17	166.68 ± 22.89	0.02*	0.68
Visit 2				
Radner Acuity	0.23 ± 0.06	0.09 ± 0.08	<0.01***	1.83
CPS 95%	0.52 ± 0.15	0.44 ± 0.20	0.04*	0.42
Maximum Reading Speed	140.50 ± 21.21	167.23 ± 14.67	<0.01***	1.64

Data = mean ± standard deviation
CPS = critical print size
Acuity/Critical print size units = LogMAR
Maximum reading speed units = words per minute

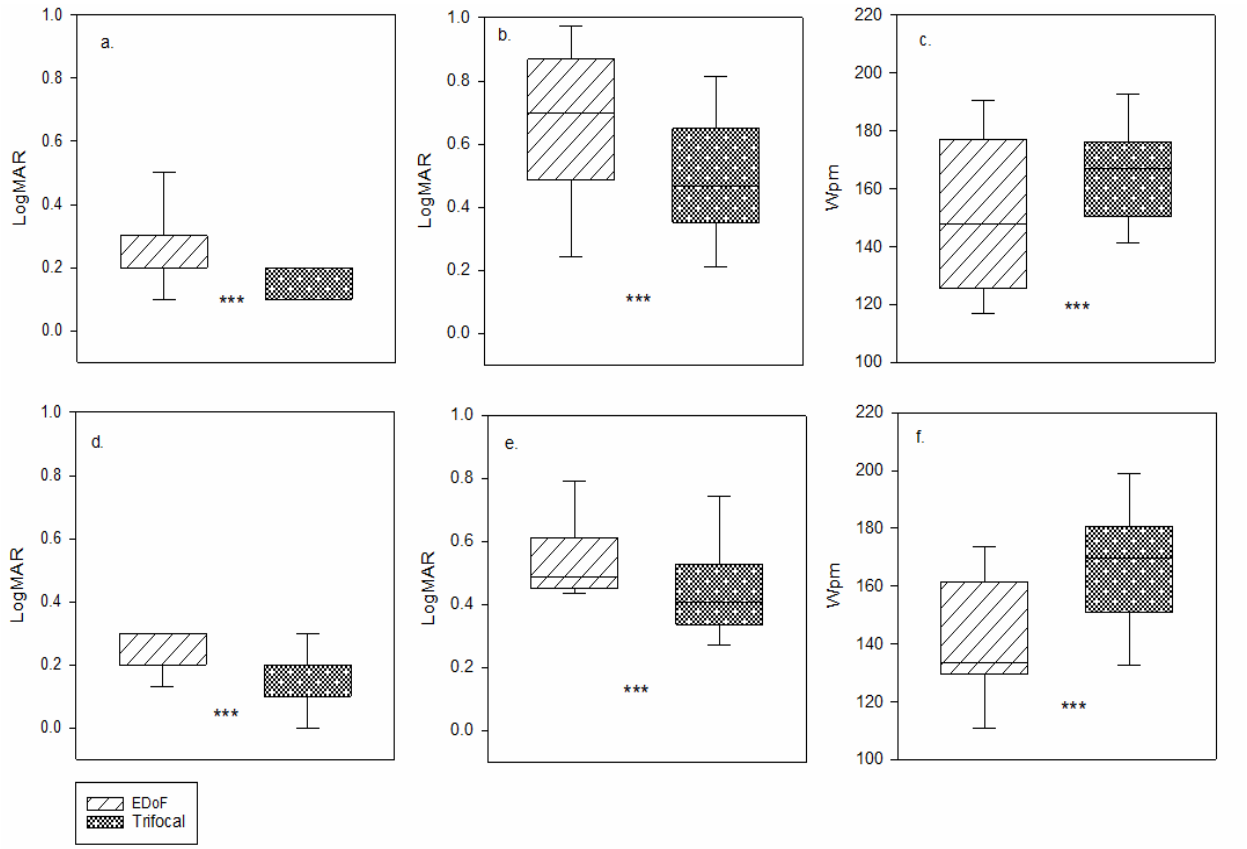


Figure 5.5: Radner reading assessment. Error bars = standard deviation

a. Visit 1 Radner Acuity
b. Visit 1 95% Critical print size
c. Visit 1 reading speed
d. Visit 2 Radner Acuity
e. Visit 2 95% Critical print size
f. Visit 2 reading speed

5.6.6 Contrast Sensitivity

Paired samples *t* tests found significant differences between monocular and binocular Pelli-Robson Contrast sensitivity within both groups ($p < 0.01$). Independent *t* tests found no significant difference monocularly ($p = 0.46$) or binocularly ($p = 0.19$) between groups at visit 1 nor Visit 2 (monocular $p = 0.08$, binocular $p = 0.35$). There were also no significant differences between visits within either group ($p>0.05$)(Figure 5.6).

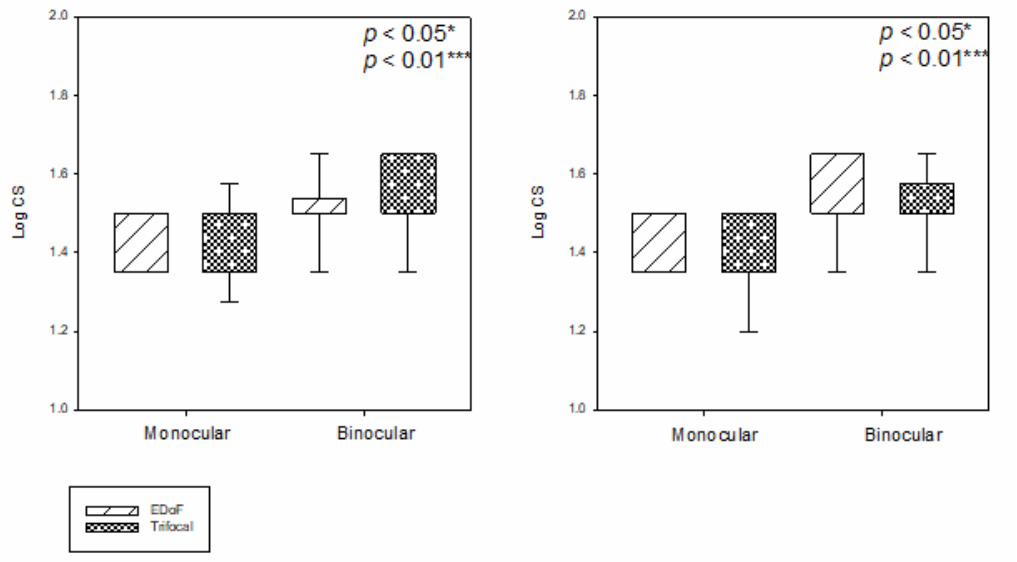


Figure 5.6: Pelli Robson contrast sensitivity. Error bars = standard deviation

a. Visit 1
b. Visit 2

No significant differences were found between groups when testing CSV-1000 in photopic conditions for 3, 6 and 12 cpd. At 18 cpd the EDoF group had significantly better contrast sensitivity at both V1 (p = 0.03) but not Visit 2 (p = 0.09) (Figure 5.7).

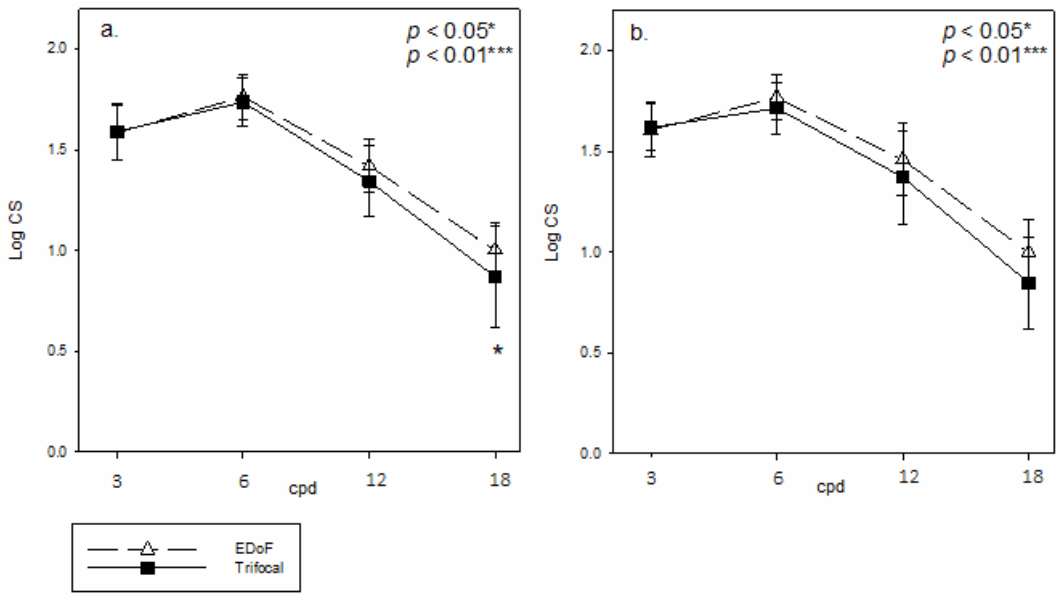


Figure 5.7: CSV-1000 contrast sensitivity. Error bars = standard deviation

a. Visit 1 b. Visit 2

5.6.7 Quality of Vision Questionnaire

Overall satisfaction was high in both groups for distance and intermediate tasks (>95%). Only 70% of the EDoF group reported satisfaction with their unaided near vision, compared to 100% satisfaction in the trifocal group (Figure 5.8).

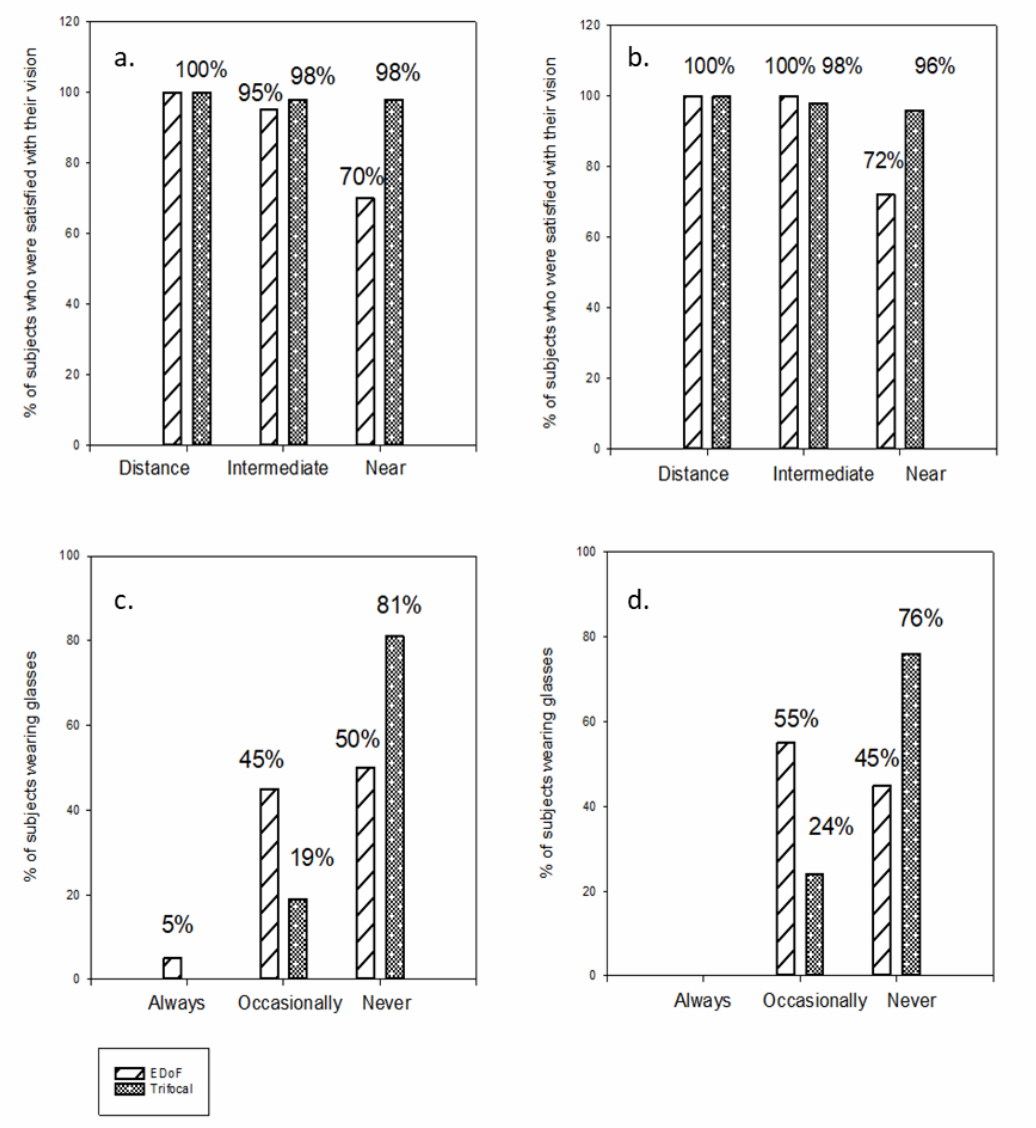


Figure 5.8: Spectacle independence

a. V1 Satisfaction
b. V2 Satisfaction
c. V1 Spectacle wear
d. V2 Spectacle wear

In the trifocal group, 81% of subjects were entirely spectacle independent, the remaining 20% wore reading spectacles occasionally only (Figure 5.8c). In the EDoF group, only 50% of patients were entirely spectacle independent, 1 subject wore varifocal spectacles full time, the remainder used reading spectacles. In both groups, spectacle independence reduced slightly by Visit 2 (Figure 5.8d).

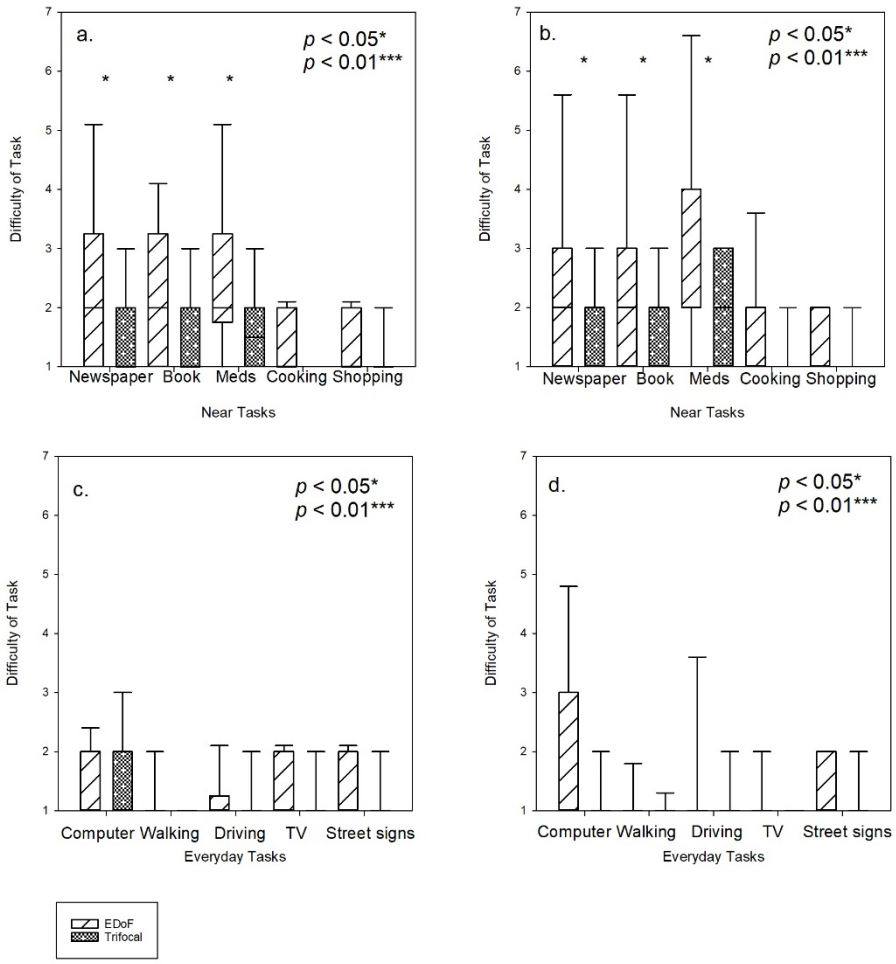


Figure 5.9: Quality of Vision Tasks. Error bars = standard deviation

a. Visit 1 Near Tasks
b. Visit 2 Near Tasks
c. Visit 1 Everyday Tasks
d. Visit 2 Everyday Tasks

Difficulty scores for reading a newspaper, book and labels on medications were less in the trifocal group at both visits (p <0.05) (Figure 5.9a and 5.9b). However, everyday tasks were similar in both groups (Figure 5.9c, 5.9d), with no statistical significance.

5.6.8 NAVQ

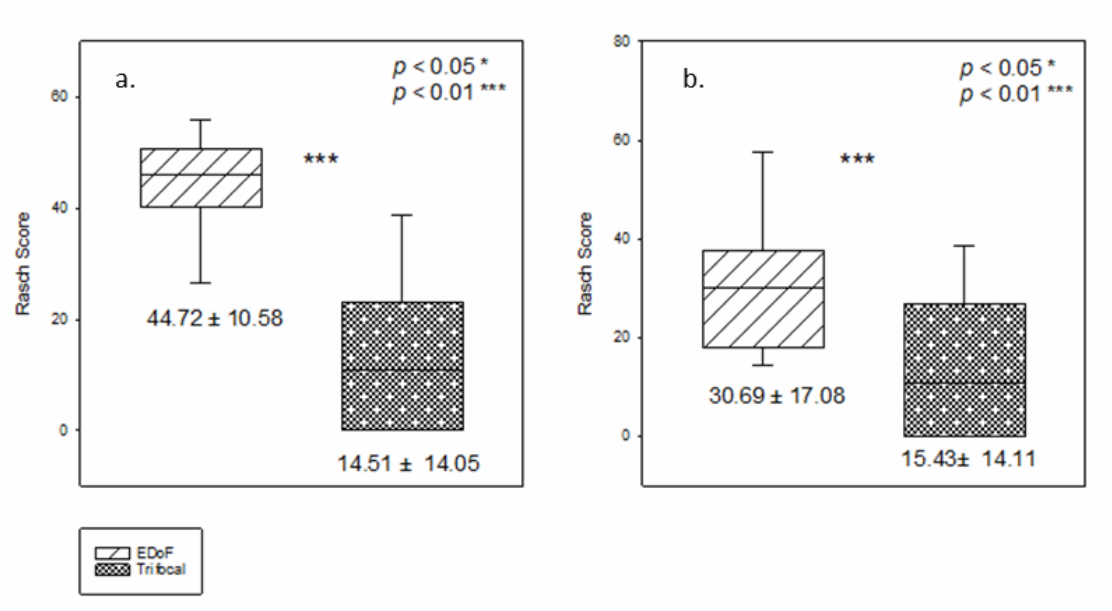


Figure 5.10: NAVQ questionnaire. Error bars = standard deviation

a. Visit 1
b. Visit 2

The NAVQ questionnaire is specific to near tasks and the trifocal group had a significantly better satisfaction score at both Visit 1(p < 0.01) and Visit 2 (p = 0.02). Both groups showed an improved NAVQ score at the second visit but this was only statistically significant in the EDoF group (p = 0.03) (Figure 5.10).

5.6.9 Dysphotopsia

There were no significant differences between groups in difficulty rating due to night vision (Figure 5.11).

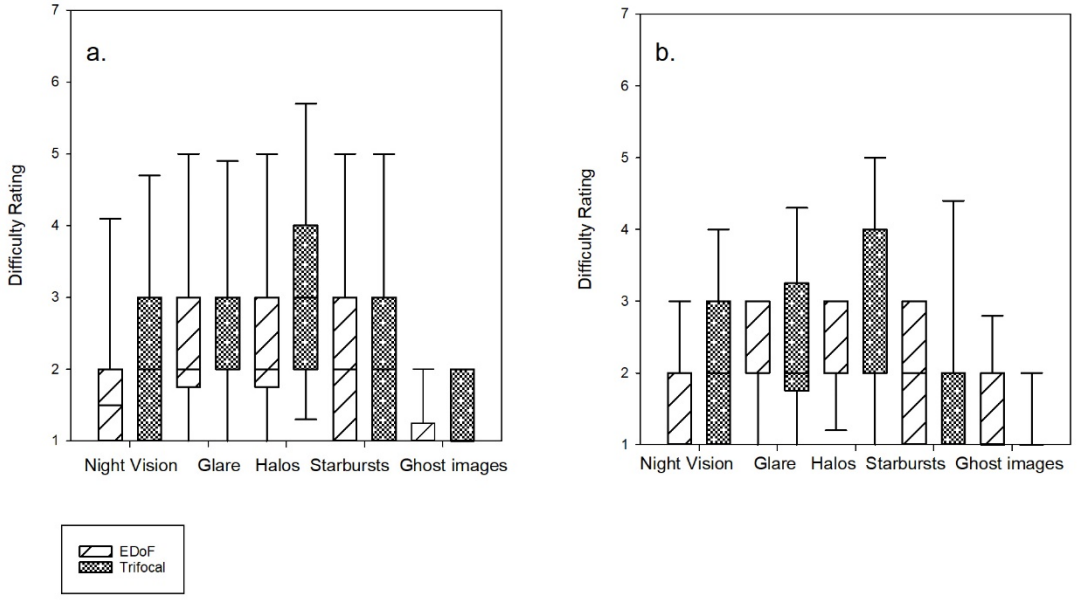


Figure 5.11: Night Vision**.** Error bars = standard deviation

a. Visit 1
b. Visit 2

Scores from 0 (nil) to 100 (maximum) were given for both Halo size and Halo brightness, both size ($p = 0.01$) and brightness ($p < 0.01$) were significantly greater in the trifocal group at V1 but there were no significant differences at V2 (size, $p = 0.51$)(brightness $p = 0.73$).

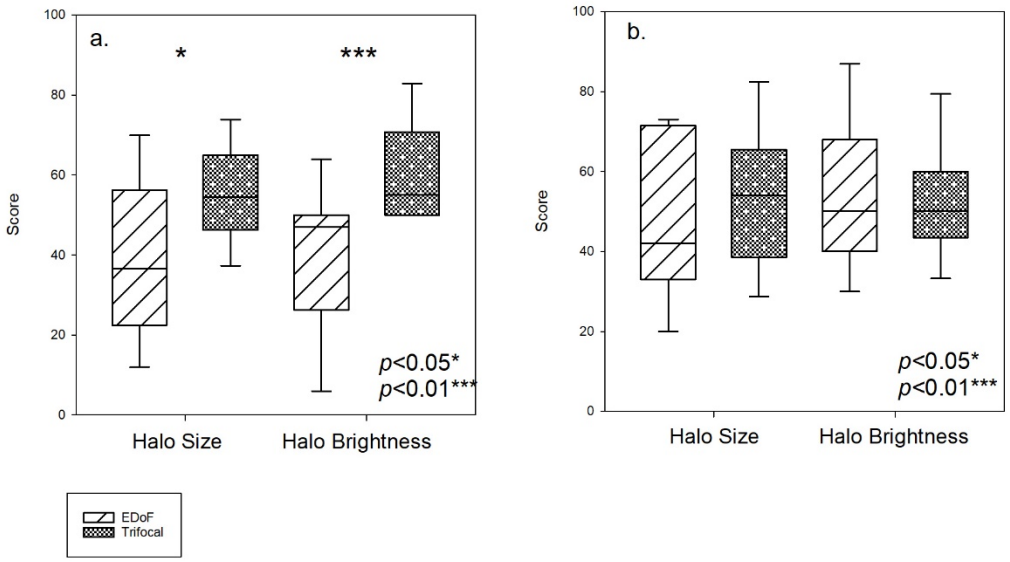


Figure 5.12: Halo Simulator Scores**.** Error bars = standard deviation

a. Visit 1
b. Visit 2

5.7 Discussion

Trifocal MIOLs are designed to reduce spectacle dependence by providing good distance, intermediate and near vision. EDoF IOLs are based on the ethos that distance and intermediate vision are prioritised to minimise the effect on contrast and dysphotopsia. As such, it is important to evaluate clinically the effects of these design differences over time to evaluate the effect on vision. This study is the first to evaluate the visual outcomes of these lenses over a one-year post-operative period and highlights the effect this longer adaption period has on vision.

Excellent distance visual acuity was achieved in both groups and no significant differences were found in distance visual acuity measures. All subjects were satisfied with their distance vision at visit 1 and visit 2. The only difference observed in contrast sensitivity occurred in the 3-6 month visit at 18cpd where the EDoF cohort performed better. This result is supported by

Mencucci and colleagues who also found a significant difference at 18cpd at the three-month timeline (Mencucci et al., 2018). Interestingly, by the one year post-operative visit, this observation was no longer present and contrast sensitivity was similar even at this high spatial frequency. Similarly, at 3-6 months, both halo size and brightness were both significantly greater in the trifocal group; however by one-year visit these values were also similar between cohorts. These striking changes for CS and halo over time are compelling evidence for an increasing occurrence of neural adaptation in the trifocal cohort over a one-year post-operative period.

Within the current study, there was no significant difference in the perceived difficulty in night vision described by subjects, yet the halo simulation scores were greater at V1 in the trifocal group. By the one year visit, the simulation scores were similar. We also saw an improvement in simulator scores in Chapter 4, with the bifocal group, suggestive of neuroadaptation. These findings concur with previous studies which suggest a neuroadaptive effect in MIOLs (Rosa et al., 2017a, Braga-Mele et al., 2014). However, such a response was not noted in the EDoF group. Previous bench studies have shown contradictory evidence of halo: Gatinel's study (Gatinel and Loicq, 2016) found that halo characteristics were similar in EDoF, bifocal and trifocal IOLs, yet Yoo (Yoo et al., 2018) suggested that the halo pattern of these EDoF IOLs is actually comparable to monofocal IOLs. Clinically, Monaco (Monaco et al., 2017) found no difference in photic phenomena between an EDoF and a trifocal group, yet Rodov (Rodov et al., 2019) found increased levels in trifocals . To date, there is no firm agreement in the literature that the dysphotopsia experienced in trifocals is more likely to be symptomatic than in EDoF IOLS. This variability could be related to testing methods, direct questions are more likely to result in a report of glare/halos than indirect questions and a patient's personality traits and expectations will influence how they cope with such visual disturbances. This could

also be due to variations in post-operative duration, as this study has illustrated variation in such results over time.

The present study demonstrated improved intermediate performance in the EDoF cohort when examining the results of the defocus curve: Both the intermediate area of focus (between -0.50 and -2.00D) (2m and 50cm) and vision with -1.50D defocus (according to the direct comparison method) were better when compared to the trifocal cohort. Intermediate visual acuity testing failed to illicit such differences with both cohorts demonstrating similar values. In comparison Webers' tested intermediate VA at 66cm, Mencucci used 80cm and this study tested at 70cm (Mencucci et al., 2018, Webers et al., 2020). Mencucci (Mencucci et al., 2018) also found that intermediate vision was similar whilst Webers' study found UIVA to be better in the EDoF group, however they themselves questioned whether the 0.03 LogMAR difference, was clinically relevant, despite being statistically significant (Webers et al., 2020). This discrepancy in findings highlights the inadequacy of VA testing as an isolated measure as it only affords the clinician a snapshot of visual performance at a fixed distance, which may differ between studies, thus direct comparison is rendered impossible. The AT LISA trifocal is known to have 3 principle foci in its central 4.34mm optic and an asymmetrical light distribution of 50%, 20% and 30% to distance, intermediate and near respectively. Beyond 4.34mm the optic is bifocal (www.zeiss.com). In contrast, the Symfony shows greater heterogeneity in light distribution between its 2 principle foci (Chae et al., 2020). *In vitro* assessment has shown the trifocals intermediate MTF performance worsens with increasing pupil size beyond an optimal 3mm (Ruiz-Alcocer et al., 2014). Whereas, the Symfony has been shown to maintain intermediate MTF in 4.5mm apertures (Chae et al., 2020). Unfortunately, we did not measure pupil size in this cohort of patients, however it is possible that discrepancies in intermediate performance between cohorts are also influenced by pupil size.

Both unaided and best corrected near VA was significantly better with the trifocal group and this finding was confirmed by direct comparison of the defocus range and the near area of focus metric. Further affirmation of the heightened near performance is Radner reading performance and the better NAVQ score achieved in the trifocal group and greater spectacle independence. However, 50% of the EDoF group still achieved complete spectacle independence suggesting that they achieved adequate near vision for their particular lifestyle. This finding is perhaps not unexpected as this was not a randomised trial, thus subjects who chose to have an EDoF IOL were those best suited to its characteristics and likely to benefit from the intermediate VA rather than near. Higher levels of spectacle independence have been reported in other studies where a micro-monovision approach has been used with EDoF lenses (Ganesh et al., 2018, Hogarty et al., 2018, Webers et al., 2020).

The defocus profiles illustrated differences in the groups from -2.50D onwards only, thus IOLs performed similarly at -2.00D of defocus (50cm), and it is likely this is why many subjects do not require spectacles for reading. Webers' study also found differences, in favour of the trifocal, in the defocus curve from -2.50D to -4.00 despite their micromonovision approach (Webers et al., 2020). Other studies comparing the defocus curves of these IOLs, have not explored such a wide range and thus cannot be compared adequately (Ganesh et al., 2018, Palomino-Bautista et al., 2020).

Reading performance assessed with the Radner tests, highlighted improved performance in the trifocal group at all visits. This is an expected findings as this test was performed at 40cm in photopic conditions, as was visual acuity testing (Mencucci et al., 2018). Both previous studies, reported no differences in CPS, RA or MRS, this is expected when micromonovision has been targeted (Webers et al., 2020), yet somewhat incongruous in Mencucci's study as it is in direct contrast to their own UNVA and DCNVA finding (Mencucci et al., 2018).

5.8 Limitations

The present study is somewhat limited in its evaluation of these lenses as it does not investigate mesopic conditions, nor was it randomised. However it does evaluate the lenses without an additional modifications such as micromonovision. The sample sizes were unequal and this is a reflection of patient choice.

In addition, there was a marked difference in sample sizes between groups, as patients were all counselled prior to surgery on the features of both lenses, it can be assumed that near vision is an important consideration, thus more patients opted for the trifocal IOL.

5.9 Conclusion

Based on current results, we conclude that for distance and intermediate vision there is little difference between the AT LISA 839MP and the Tecnis Symfony. Despite greater intermediate performance noted with the Technis Symfony during defocus analysis, this was not reflected in patient reported outcomes. The AT LISA 839MP performs significantly better for near vision and as a result spectacle independence is increased. However, spectacle independence can be achieved using the Symfony if appropriate subjects are implanted or based on published literature a micromonovision approach is utilised. There was no detriment to contrast sensitivity demonstrable with the Trifocal compared to EDoF IOLs, and although photopic phenomena were more pronounced at the initial visit with the AT LISA 839MP, no additional perceived difficulty resulting from these halos was apparent when patients were questioned.

This study also illustrates the standardised protocol suggested in Chapter 4, can be utilised in Trifocal and EDoF also.

Thus, in summary, the primary findings of this study are:

- The Symfony provides a greater Area of focus in the intermediate range, however patient reported outcomes did not show a difference in intermediate performance
- Better near vision and greater spectacle independence are achieved with a trifocal IOL
- Longer term follow up highlights the role of neural adaptation as comparable results were found in contrast sensitivity and dysphotopsia one year post-implantation.

5.10 Supporting Publication

This Chapter forms the basis for the research paper:

Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. One-year post-operative comparison of visual function and patient satisfaction with trifocal and extended depth of focus intraocular lenses *J Refract Surg*. Under Review

Chapter 6

Randomised intra-patient comparison of closed loop and plate haptic toric intraocular lenses

OVERVIEW

Uncorrected astigmatism can reduce spectacle independence and visual outcomes following cataract surgery, thus astigmatism must be considered in surgical planning. The efficacy of a toric intraocular lens depends on sound pre-operative power calculations, precise surgical alignment and post-operative rotational stability.

This intra-patient randomised control trial compared toric IOLs of differing designs. In order to minimise variability in rotational stability that may be due to an individual's capsular bag characteristics, this study was performed intra-patient. Both rotational stability and refractive outcomes were assessed.

No significant differences in stability were found between IOLs. Refractively, both IOLs resulted in overcorrection of with the rule astigmatism and undercorrection of against the rule astigmatism. However retrospective analysis with the manufacturers updated calculator, suggests that the undercorrection found in against the rule astigmatism with the original calculations has now been remedied.

6.1 Introduction

In addition to presbyopia, uncorrected astigmatism can also reduce spectacle independence post-operatively. It is estimated that one-fifth of patients requiring cataract surgery have astigmatism of greater than 1.5 dioptres (D) and thus the correction of pre-operative astigmatism must be considered (Ostri et al., 2015). It has been shown that uncorrected astigmatism can significantly decrease visual acuity (Wolffsohn et al., 2011).

Various surgical methods are possible to correct astigmatism (Mozayan and Lee, 2014) and the use of toric intraocular lenses (TIOLs) has been shown to be reliable and repeatable.(Kessel et al., 2016, Lake et al., 2019) Efficacy of TIOLs is reliant on 3 main components; rotational stability, accurate pre-operative measurement of astigmatism and accurate calculation of appropriate TIOL power and orientation (Potvin et al., 2016, Ribeiro et al., 2019)[7].

Rotational stablility is governed by factors such as TIOL material, size, haptic design and capsular contraction. It is well known that the cylindrical power is rendered ineffective with rotation of 30° and greater rotation can result in post-operative cylinder greater than pre-operative (Felipe et al., 2011). This relationship is sinusoidal rather than linear, thus even small misalignments can result in the need for significant residual cylindrical correction (Ma and Tseng, 2008).

Several investigations have discussed rotational stability with both open loop and plate haptics, (Chang, 2008, Kessel et al., 2016, Patel et al., 1999) however there is a paucity of studies analysing closed loop torics (Alberdi et al., 2012, Khoramnia et al., 2015) This study aims to compare two differing styles of TIOL, a closed loop haptic design and a plate haptic design. The aim was to assess the IOLs using recognised methods that would provide rigorous examination

of TIOLs to ascertain any differences in rotational stablility.We hypothesise that the differing haptic design may lead to differences in rotational stability.

In addition, the effective prediction of refractive outcome, is also crucial. Many recent studies have explored the efficacy of toric calculators and the effects of anterior and posterior corneal curvature on the prediction of TIOL power.(Koch et al., 2013, Ribeiro et al., 2019, Visser et al., 2013). There are many commercially available toric calculators, many of the TIOL manufactures advocate the use of their own calculator in surgical planning. Toric calculators assume thin lens calculations. Typically, anterior corneal curvature readings are obtained from the biometer or keratometer and entered into the calculator along with refractive data. Posterior corneal astimagtism (PCA) was previously thought to induce only minimal refractive astigmatism and thus could be discounted from toric calculations. (Abulafia et al., 2016). Indeed, at the time of recruitment for this study, none of the manufacturers calculators accounted for posterior corneal astigmatism (Goggin et al., 2015). However, studies have since shown that failing to consider total corneal astigmatism (TCA) can lead to an increased error in post-operative residual refractive astigmatism (Goggin et al., 2015, Koch et al., 2013, Savini and Naeser, 2015). Koch (Koch et al., 2012) found that in the majority of his subjects the posterior corneal astigmatism had a steep vertical meridian, hence with-the-rule (WTR). This can lead to an underestimation of total corneal astigmatism in the horizontal meridain, thus toric calculators will overcorrect in WTR astigmatism and undercorrect in ATR astigmatism (Goggin et al., 2015, Koch et al., 2012, Savini and Naeser, 2015). There are now nomograms available (Baylor nomogram or Barrett calculator) which predict posterior corneal astigmatism from anterior corneal astigmatism (Abulafia et al., 2015, Koch et al., 2013) Both manufacturers included in this study have made updates to their calculator since the recruitment stage of this study.

Therefore, we retrospectively, carried out toric calculations with the new calculators also to establish if their ability to accurately predict residual refractive error had improved.

The primary aims of this study are:

- To compare rotational stability with two differing haptic designs
- To compare refractive outcomes
- To assess the reliability of manufacturers toric calculators

6.2 Study Design

This study was a prospective, randomised comparative, contralateral eye clinical trial. The study protocol adheres to the Declaration of Helsinki and ethical approval was obtained prior to commencement of the trial (Ref 15/SW/0025, IRAS 168791)(Appendix 1). The study was registered with clinicaltrails.gov (NCT02264457) and informed consent was obtained from all subjects. No modifications to the protocol or outcome measures were made during the study. Primary outcome measures were unaided and best corrected distance visual acuity, residual refraction and TIOL rotation.

6.2.1 Patient Selection

Between December 2015 and March 2018, thirty subjects were recruited from routine cataract clinics at a local hospital on a consecutive – if – eligible (consecutive patients meeting the inclusion criteria) basis according to the inclusion/exclusion criteria (Table 6.1). All subjects

were initially reviewed by a consultant ophthalmic surgeon, clinical examination included a dilated fundus examination, including OCT if macular pathology was suspected. Thorough slit lamp examination of the ocular surface and anterior segment was performed and ocular lubricants (hyaluronic acid based eye drops) commenced if minor ocular surface dryness was noted. Moderate to severe ocular surface disease resulted in exclusion. Corneal topography was performed to exclude irregular astigmatism.

Table 6.1: Inclusion/Exclusion Criteria

Inclusion	Exclusion
Age related cataract requiring bilateral cataract surgery with phacoemulsification	Irregular astigmatism
Participants requiring primary IOL implantation	Previous intraocular and/or corneal surgery
Participants with a potential corrected visual acuity of 0.3 LogMAR or better on clinical assessment in both eyes	Subjects using a systemic medication that is known to cause ocular side effects
Subjects with clear intraocular media and normal anterior segment other than cataract	Subjects participating in a concurrent clinical trial or if they have participated in an ophthalmology clinical trial within the last 30 days
Participants aged 50-75 years	Dilated pupil < 5mm
> 1.50D of preoperative corneal astigmatism bilaterally	Subjects who could not make an informed consent
Requiring an IOL within the power range of : Spherical +6.00 to +30.00D Cylindrical +1.00 to +6.00D	Retinal pathology

Risks and benefits of surgery were explained, and all patients were given the opportunity to ask questions. Eligible subjects were provided with a verbal explanation of the study and issued

with further written information to consider in their own time. Informed consent was obtained and consent forms recorded in the subject's medical record.

6.2.2 Randomisation

The allocation of IOLs was randomly assigned based on first eye surgery and was masked to both the participant and the investigator conducting the post-operative study assessments. On enrolment, a study number was assigned to each subject. The allocation of lenses for all subjects was randomized using Microsoft® Excel® 2013 (Microsoft Corporation, California, USA). The investigation used blocked randomization with a 1:1 allocation ratio to guarantee that the distribution of IOL assignment was equal according to the first eye. Following allocation of the subject number, the unmasked surgeons and theatre staff accessed the randomization log and a series of sealed opaque envelopes that described which lenses were to be implanted (plate or closed loop).

- Group A: First eye Closed Loop haptic IOL
- Group B: First eye Plate haptic IOL

The manufacturer's own toric calculators were used for each lens, using the data collected from the biometry and refraction. The same surgeon implanted both IOLs for an individual subject.

6.2.3 Intraocular Lenses

Two differing IOL designs were utilised, a plate haptic (Zeiss AT Torbi 709M) and a closed loop haptic (Rayner T *flex* 623T). (Table 6.2)(Figure 6.1).

Table 6.2: Characteristics of the Intraocular Lenses		
Maufacturer	**Rayner** T *flex* 623T	**Zeiss AT Torbi 709M**
Haptic Design	Closed loop haptic	Plate haptic
Material	Hydrophilic acrylic	Hydrophilic acrylic with a hydrophobic surface
Aspheric	Yes	Yes
Sphere Range **Cyl Range**	-10.00 to +35.00D (0.50D steps) +1.00 to +11.00D (0.25D steps)	-10.00 to +32.00D (0.50D steps) +1.00 to +12.00D (0.50D steps)
Optic Diameter	6.25mm	6mm biconvex
Overall Length	12.50mm	11.00mm
Haptic	Closed loop-haptic	Plate Haptic
Pre-loaded	Yes (in some powers)	Yes (in some powers)

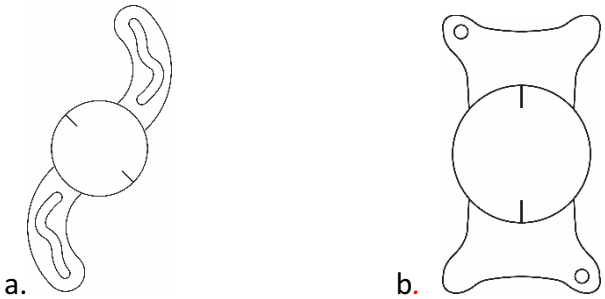


Figure 6.1: Toric IOL Designs

a. Closed Loop haptic IOL
b. Plate haptic IOL

Both IOLs have 0° angulation, as previous literature suggests that angulation can increase axial movement of the IOL post-operatively (Petternel et al., 2004).

6.3 Surgical Technique

All surgeries were performed by one of two experienced consultant ophthalmic surgeons (RA and HK) using small incision phacoemulsification. The same surgeon operated on both eyes of

a subject. In each case, a 2.4mm clear corneal incision was located according to the steepest corneal meridian where possible. The OVD used was Hydroxypropyl Methylcellulose (HPMC) during phacoemulsification, and then the cohesive OVD, Healon, during IOL insertion to facilitate easier removal from behind the IOL. The pre- and post-operative medication regime was the same regardless of surgeon. Second eye surgery occurred within 2 weeks of first eye surgery.

6.3.1 Pre-Surgery Medication

Anaesthesia was achieved by topical administration of Minims®Proxymetacaine hydrochloride 0.5% (Bausch & Lomb) eye drops prior to and during surgery. Pupil dilation was achieved by topical application of the mydriatic agents, Minims®Tropicamide 1% (Bausch & Lomb) and Minims®Phenylephrine 2.5% (Bausch & Lomb) and oral administration of 250mg Acetazolamide was also implemented as routine practice.

6.3.2 Toric Marking Technique

The vertical and horizontal axes were marked prior to surgery (0°, 90° and 180°) with the subject upright at the slit lamp using a surgical marker pen to compensate for the cyclotorsion resultant from a supine position. A sterile ink pen was used to create these markings at the limbus. The axis for toric IOL alignment was also marked at this time. During surgery the TIOL is rotated to the correct axis and the position validated with a Mendez ring. A previous study has indicated that this method is accurate to within 4° of optimal alignment (Visser et al., 2011a, Webers et al., 2017)

6.3.3 Post-Surgical Medication and Advice

Following surgery, the subjects were instructed to use Tobradex 3mg/ml/1mg/ml (Novartis) four times daily for four weeks following surgery. Standard post-operative advice was provided verbally and as an information leaflet.

6.4 Method

6.4.1 Study Visits

Post-operatively each subject had base line slit lamp imaging within 1 hour of surgery. Four study visits (V1: Day 1-2, V2: Week 1-2, V3: Month 1-2, and V4: Month 3-4post-surgery) were required to complete the study. At each visit slit lamp imaging and photography was repeated. Refraction and visual acuity assessment for each eye were completed in photopic light conditions of illuminance 120cd/m^2 and luminance of 95 lux. The study measures are summarised in Table 6.3 below.

Table 6.3: Study Measures

Outcome Measure	Method
Distance Vision and VA	6m LogMAR computerised chart (Thomson software solutions) Monocular and Binocular
Subjective Refraction	6m LogMAR computerised Chart (Thomson software solutions)
AutoRefractor/Keratometer	Topcon KR-8000PA Objective measurement of refraction Keratometry
Biometry	Haag-Streit LENSTAR LS-900
Intraocular Pressure	Goldmann Tonometry
Photography	Dilated slit lamp retro-illuminated images of toric markings Dilated 1% Tropicamide and 2.5% Phenylephrine

6.4.2 Refraction

A combination of objective and subjective techniques were used to determine the residual refractive error. The Topcon KR-800 (Topcon Corporation, Tokyo, Japan) autorefractor gave an objective measure which was then refined by subjective refraction techniques to maximise plus for best corrected acuity using the Thomson Chart 2000 (Thomson Software Solutions, Hatfield, Herts, UK). The distance refraction was then used to measured best distance corrected visual acuity.

6.4.3 Visual Acuity

At each visit, monocular and binocular LogMAR acuities for unaided (UDVA) and best distance corrected (CDVA) were measured using the Thomson Test Chart 2000 at a testing distance of 6m. Sloan letters were used consistent with ETDRS protocols (Ferris et al., 1982, Hazel and Elliott, 2002, Rosser et al., 2003, Shah et al., 2010, Williams et al., 2008). Letters can easily be randomised to avoid learning effects and no conversion of VA is required.

6.4.4 Keratometry

Corneal curvature was measured using the KR8000PA (Topcon, Tokyo, Japan) which is a combination auto-refractor and keratometer/corneal topographer. It uses infrared illumination of target mires and infrared photodetectors to measure the image size and compute corneal curvature in conjunction with 10 placido rings). It has previously been shown to provide good reliability and repeatability (Mehravaran et al., 2014). The topography allowed us to screen for irregular astigmatism.

6.4.5 Biometry

The LenStar Biometer (Haag-Streit AG, Koeniz, Switzerland) was used at each visit, to establish corneal curvature and actual lens position. The LenStar uses optical low coherence reflectometry (OLCR) and dual zone keratometry, at 32 (each comprised of 4 measurements) point pattern over 2 concentric rings at 1.65mm and 2.30mm. This results is a total of 640 measurements if the recommended 5 repeat measurements are taken by clinician (Hill et al., 2011, Reitblat et al., 2016).

6.4.6 Tonometry

Goldmann applanation tonometry was performed at each visit. Increased IOP post-operatively can be indicative of retained OVD and this can result in early TIOL rotation (Kaur et al., 2017, Ruhswurm et al., 2000).

6.4.7 Slit lamp photography

Analysis of the photographs was carried out using specialised software from LabView (National Instruments, Austin, TX, USA) and following established methods (Wolffsohn and Buckhurst, 2010). Retro-illuminated images were taken at all visits, in order to ascertain the axis of the TIOL markings. In order, to ensure that head rotation was accounted for, 4 identifiable landmarks (iris architecture or conjunctival vessels/pigmentation) were also marked in each image. (Figure 6.2)

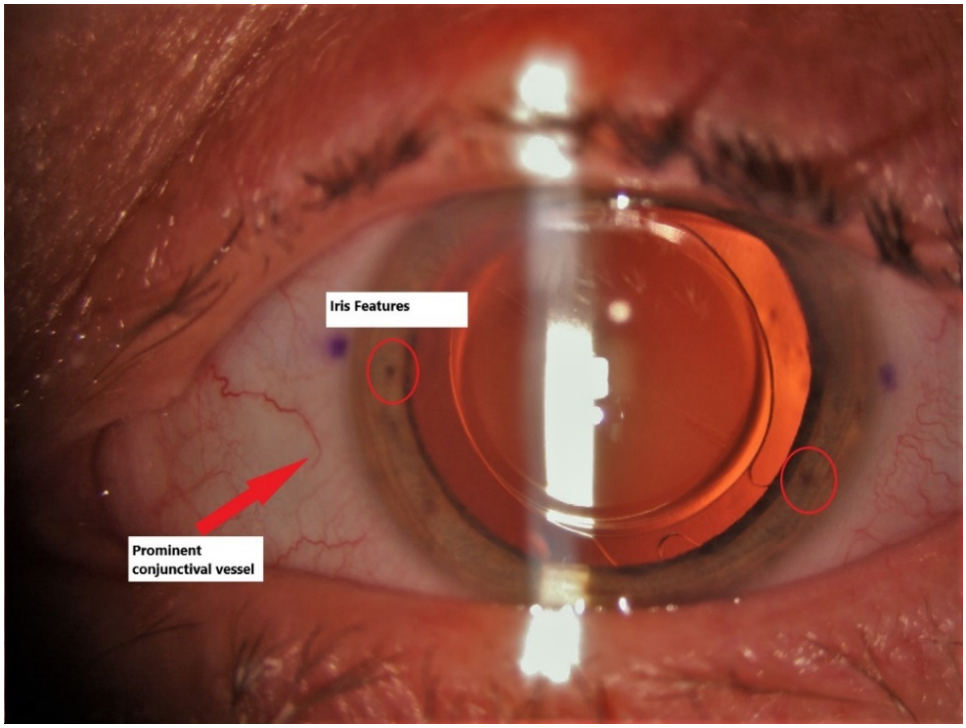


Figure 6.2: Example of identifiable landmarks

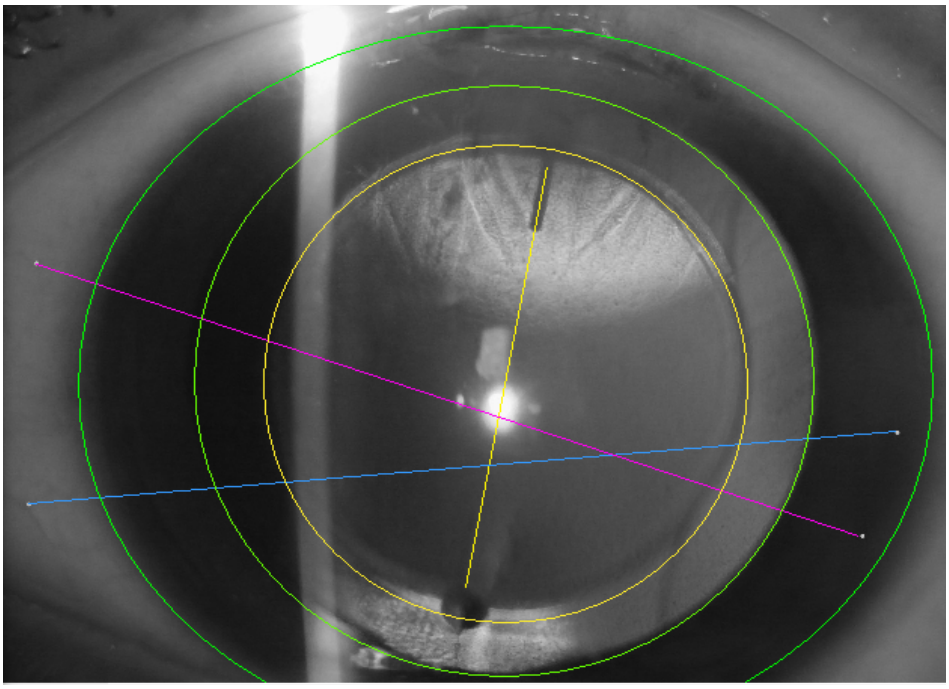


Figure 6.3: Example of TIOL photography and analysis using LabView software to highlight, pupil margin, optic margin, toric markings and 4 conjunctival or iris features

A line was drawn between markings on opposite sides of the pupil and the angles calculated (Figure 6.3). The difference in these two angles was considered the consistency angle and ensures that images can be compared between visits and head rotation accounted for.

6.5 Statistical Analysis

All statistical analysis was performed using SPSS, Version 24 (SPSS, IBM, Armonk, NY, USA). Details of specific statistical analysis for each measure follow below. In all cases a p value of <0.05 was considered statistically significant.

6.5.1 Sample Size

A Priori power analysis comparing two dependent means was calculated using G*Power 3 (Heinrick Heine, University of Dusseldorf, Germany)(Faul et al., 2007); a sample size of 26 subjects was required based on a moderate effect size 0.6; alpha = 0.05 and beta = 0.20 (80% power). To account for potential dropouts a total of 30 subjects were recruited.

6.5.2 Normality

All data were tested for normality using the Shapiro-Wilks test and visual examination of histogram plots. Parametric testing was used when the data followed a normal distribution.

6.5.3 Patient demographics

Independent *t* test were used to check for similarities in the patient demographics. Also paired *t* tests were used to check for similarity between eyes.

6.5.4 Visual Acuity

Repeated measures ANOVA were used to assess post-operative visual acuity within groups between visits and Two-Way repeated measures ANOVA to assess VA between groups at each visit.

6.5.5 Astigmatic change

Astigmatic change was analysed using the Alpins method (Alpins, 1993). Cylindrical power and axis were converted to vectors (J_0 and J_{45}) as discussed in Chapter 4 (**Equation 4.2** and **4.3**).

Target induced astigmatism (TIA) is the astigmatic correction predicted to occur with a given TIOL and was calculated with **Equation 6.1**.

$$TIA = \sqrt{((PreOp\ J_0\ - Predicted\ residual\ J_0)^2\ + (\ PreOp\ J_{45} - Predicted\ residual\ J_{45})^2)}$$

Equation 6.1: Target induced astigmatism

Surgically induced astigmatism (SIA) is the astigmatic correction achieved post-operatively, and calculated as **Equation 6.2**.

$$SIA = \sqrt{((PreOp\ J_0\ - PostOp\ J_0)^2\ + (\ PreOp\ J_{45} - PostOp\ J_{45})^2)}$$

Equation 6.2: Surgically induced astigmatism

The Correction index (CI) is the ratio of SIA to TIA (**Equation 6.3**) and difference vector is the difference between TIA and SIA (**Equation 6.4**).

$$CI = \frac{SIA}{TIA}$$

Equation 6.3: Correction Index

$$Difference\ Vector = TIA - SIA$$

Equation 6.4: Difference Vector

Correlation between SIA and TIA was assessed and dependent *t*-tests were used to analyse the remaining metrics in the two groups. Where no significant differences were found, *post hoc* power calculations were performed.

6.6 Results

Thirty subjects were recruited and twenty-six subjects completed the study (**Figure 6.4**). Two subjects had surgical complications in one eye (posterior capsular rupture) resulting in a monofocal sulcus IOL implantations and were thus withdrawn from the study. One subject died (myocardial infarction) prior to second eye implantation and one subject withdrew prior to second eye surgery due to undisclosed personal reasons.

The results are reported in accordance with the consort guidelines for randomised control trials (Moher et al., 2010).

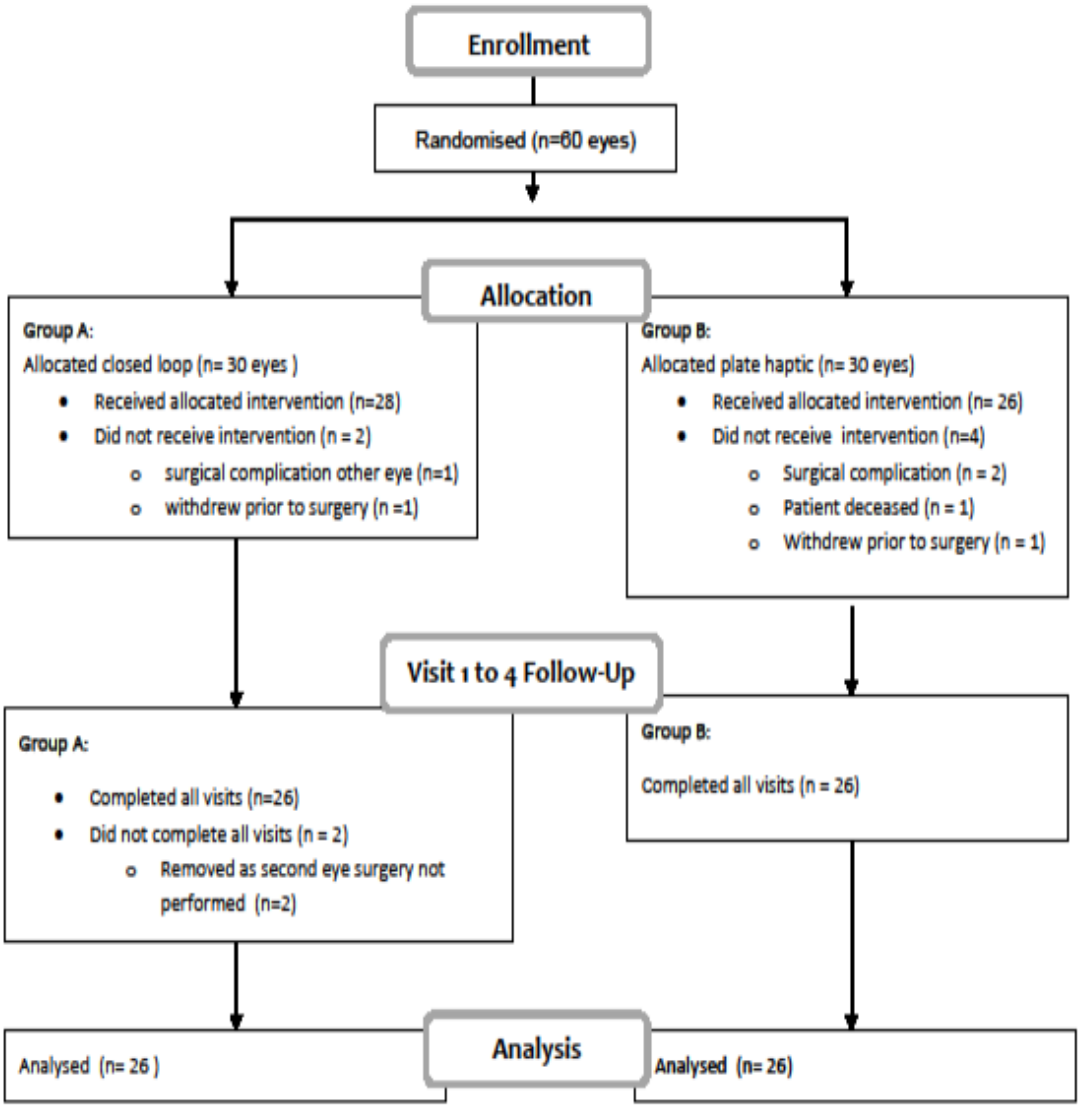


Figure 6.4 CONSORT Subject Flowchart

Of the 52 eyes, 4 IOLs required repositioning post-surgery (2 closed loop and 2 plate haptic) due to misalignment > 10 °, this misalignment was noted at V1 and intervention occurred

within 14 days. One subject (closed loop) opted out of further surgery but the remainder underwent successful realignment. This initial misalignment has been excluded from the analysis of outcomes and will be considered separately in Section 6.6.11.

6.6.1 Patient Demographics

There were no significant differences in any measures pre-operatively (Table 6.4).

Table 6.4: Patient Demographics

			p
Male/Female	14/12		
Mean Age (yrs)	68.90 ± 7.76		
Range (yrs)	50 - 75		
	Closed Loop Haptic (all eyes)	Plate Haptic (all eyes)	
Eyes	n =26	n = 26	
Pre-Op Refractive Error (DS)			
Spherical Equivalent Range	-16.00 to + 4.00	-13.13 to + 3.75	
MSE	-2.53 ± 5.02	-2.49 ± 4.87	0.76
J0	-0.37 ± 2.05	-0.58 ± 2.43	0.82
J45	0.01 ± 1.39	-0.31 ± 1.13	0.23
Pre-Op Visual Acuity (logMAR)			
CDVA	0.32 ± 0.15	0.36 ± 0.17	0.15
IOL Power (D)			
Sphere Range	6 to 25	6 to 26	
Mean	16.5 ± 5.16	15.95 ± 4.95	0.69
Cyl Range	1 to 4.5	1 to 5.5	
Mean	2.69 ± 0.97	2.88 ± 1.17	0.47

Data are mean ± Standard deviation
CDVA = Corrected distance visual acuity, IOL = Intraocular lens, J0 = cylindrical effect at 180°, J45 = cylindrical effect at 45° ,MSE = Manifest spherical equivalent

There were no significant differences in pre-operative corneal curvature, axial length or anterior chamber between the Closed Loop and Plate group ($p < 0.01$) (Table 6.5). This was expected as this was a contralateral eye study (Ray and O'Day, 1985).

Table 6.5: Biometry Measurements			
	Closed Loop	Plate	*p*
K1	42.48 ± 1.42	42.34 ± 1.45	0.10
K2	44.86 ± 1.48	45.00 ± 1.55	0.26
Anterior Chamber Depth	3.22 ± 0.50	3.13 ± 0.47	0.05
Axial Length	24.62 ± 1.82	24.55 ± 1.86	0.41
Data = Mean ± standard deviation			

There were no significant differences between groups for pre-operative astigmatism (p=0.303) (**Figure 6.5**).

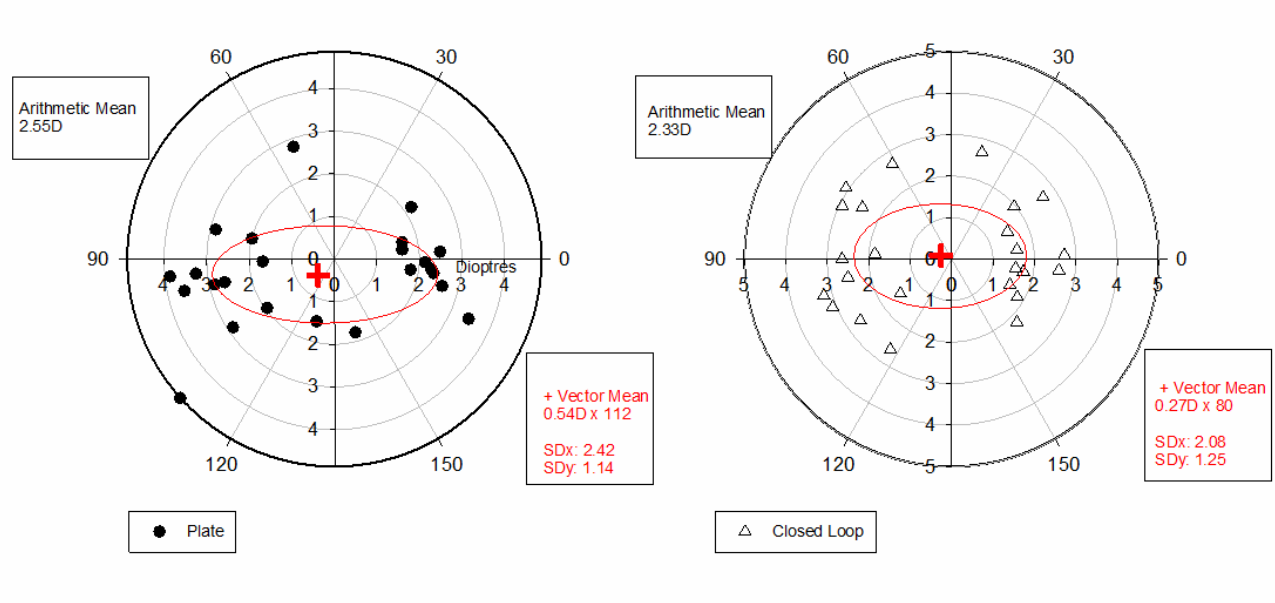


Figure 6.5: Pre-Operative Astigmatism

6.6.2 Corneal Astigmatism

Correlation between the two methods of keratometry (LenStar and KR-8000) was high in both groups (**Figure 6.6**), Plate, R = 0.959, p <0.01 and Closed Loop, R = 0.961, p <0.01. Therefore, only corneal curvature measurements from the LenStar are used in further analysis.

There were no significant differences in corneal curvature between groups. There were no significant changes in corneal curvature (K1 and K2) between visits, nor did post-operative corneal curvature vary significantly from pre-operative in either the Closed Loop ($F_{1,4}$ = 1.39, p = 0.24) or Plate group ($F_{1,4}$ = 1.54, p = 0.20).

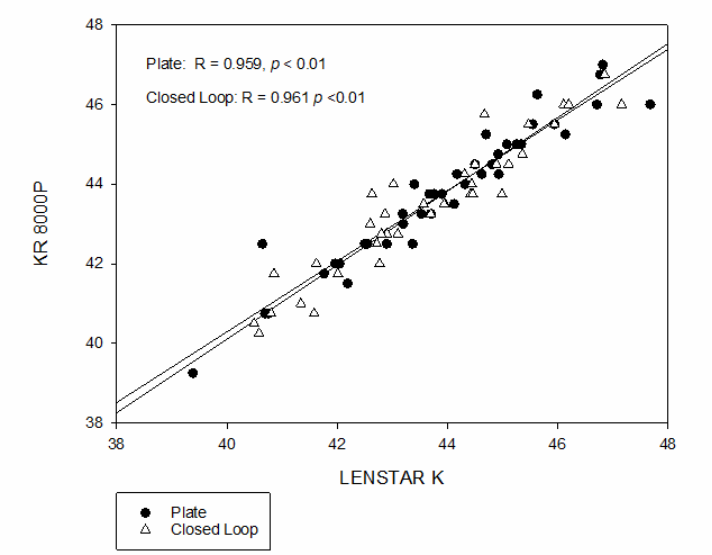


Figure 6.6: Keratometry Methods

6.6.3 Visual Acuity

At all study visits no significant differences in UDVA, F_3 = 0.488, p = 0.420 (**Table 6.6, Figure 6.7a**) or CDVA, F_4 = 0.952, p = 0.435 (**Table 6.6, Figure 6.7b**) was noted for the two different haptic groups, nor were there any significant differences between study visits in either IOL group.

Table 6.6: Visual Acuity						
Visits	Closed Loop		Plate		*p*	
	UDVA	CDVA	UDVA	CDVA	UDVA	CDVA
V1	0.20 ± 0.15	0.11 ± 0.10	0.23 ± 0.17	0.12 ± 0.13	0.684	0.289
V2	0.20 ± 0.13	0.05 ± 0.06	0.17 ± 0.15	0.05 ± 0.08	0.372	0.895
V3	0.16 ± 0.12	0.05 ± 0.07	0.17 ± 0.16	0.05 ± 0.06	0.905	0.825
V4	0.06 ± 0.06	0.03 ± 0.05	0.11 ± 0.11	0.03 ± 0.06	0.06	0.764
Mean ± Standard Deviation LogMAR						

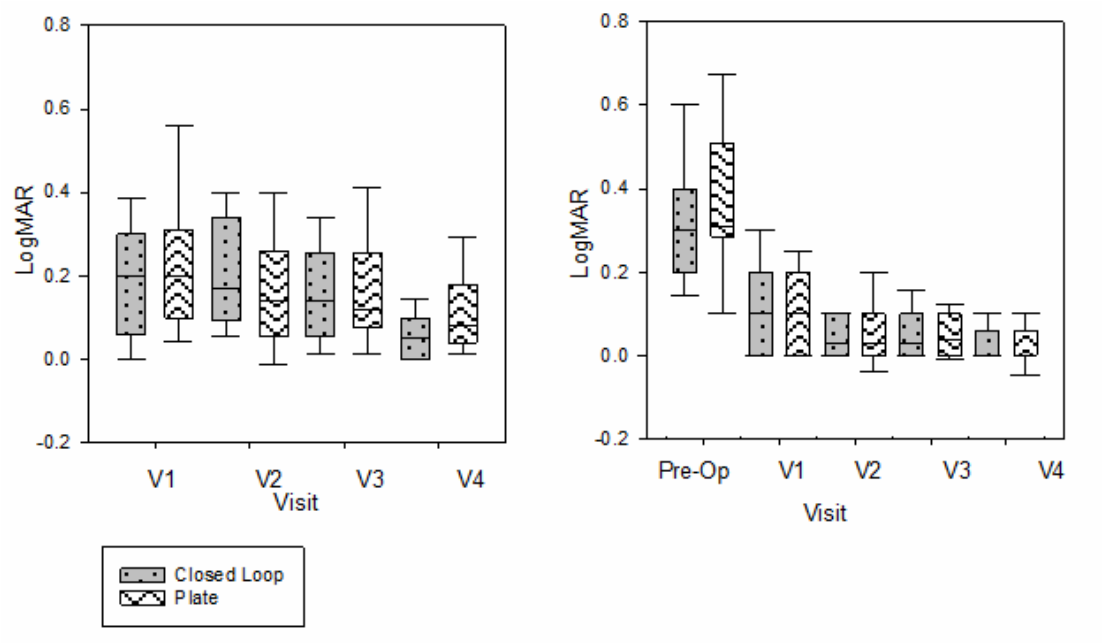


Figure 6.7: Visual Acuity. Error bars = standard deviation

a) UDVA b) CDVA

6.6.4 Post-operative Astigmatism

There was a significant improvement in astigmatic refractive error post-operatively in both groups (p<0.01). No significant different was found between the IOL haptic groups for final post-operative astigmatism at V4 (p=0.465) (**Figure 6.8**).

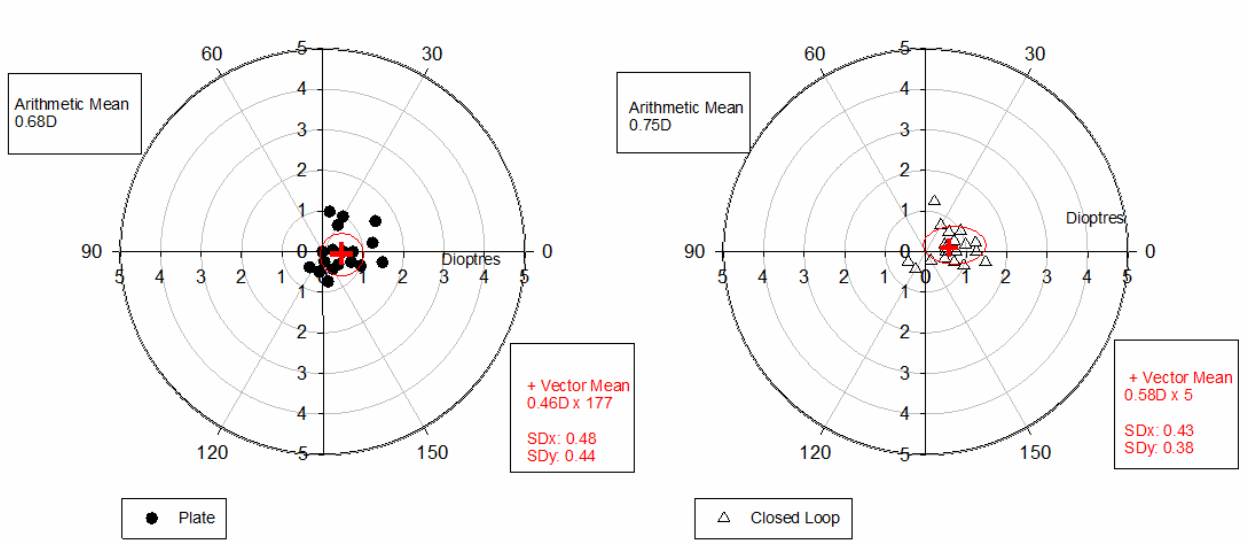


Figure 6.8*:* Visit 4 Astigmatism

6.6.5 Spherical Equivalent

Spherical Equivalent refraction accuracy compares the predicted residual spherical equivalent and the actual V4 spherical equivalent (**Figure 6.9**); a significant difference was evident for both the plate (p = 0.012) and closed loop (p = 0.009) haptic IOL groups. Correlation between predicted residual spherical equivalent and actual was R = 0.520 plate group and R = 0.383 closed loop.

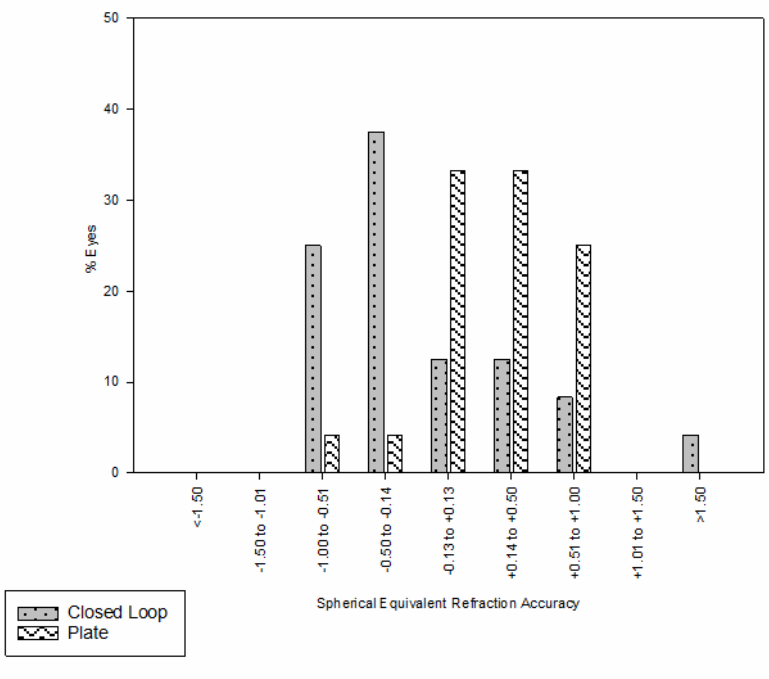


Figure 6.9*:* Spherical Equivalent Refraction Accuracy, percentage of eyes within each range

6.6.6 Target and Surgically Induced Astigmatism

Target Induced astigmatism (TIA) is the predicted astigmatic correction and surgically induced astigmatism (SIA) is the astigmatic correction actually achieved post-operatively. There was no significant different in SIA between visits in either groups, thus V4 data is used from this point forward (Table 6.7).

Table 6.7: Post-operative Sugically Induced Astigmatism

	V1	V2	V3	V4	*p*
Closed Loop	2.71 ± 1.21	2.41 ± 1.01	2.28 ± 1.02	2.30 ± 0.99	V1-V2 0.10 V2-V3 0.09 V3-V4 0.97
Plate	2.64 ± 1.23	2.47 ± 1.15	2.46 ± 1.29	2.34 ± 1.26	V1-V2 0.35 V2-V3 0.95 V3-V4 0.06
Data = Mean ± standard deviation					

The absolute TIA was similar between the two groups (p = 0.565, plate haptic 2.39±0.91, closed loop 2.24±0.56) as was the SIA (p = 0.870, plate haptic 2.34±1.26, closed loop haptic 2.30±0.98) (**Figure 6.10 and 6.11**).

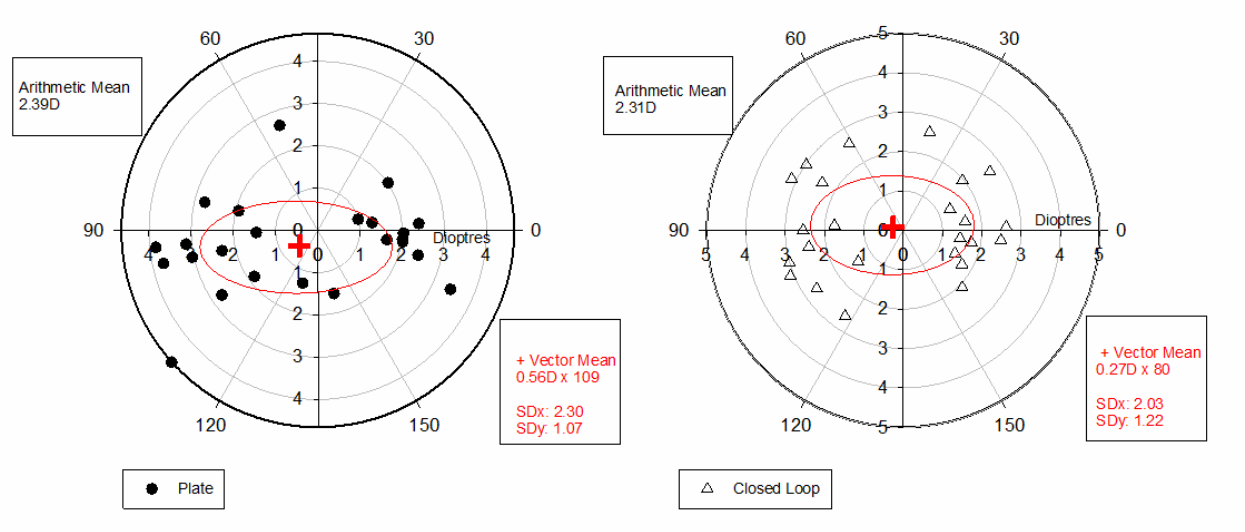


Figure 6.10: Target Induced Astigmatism

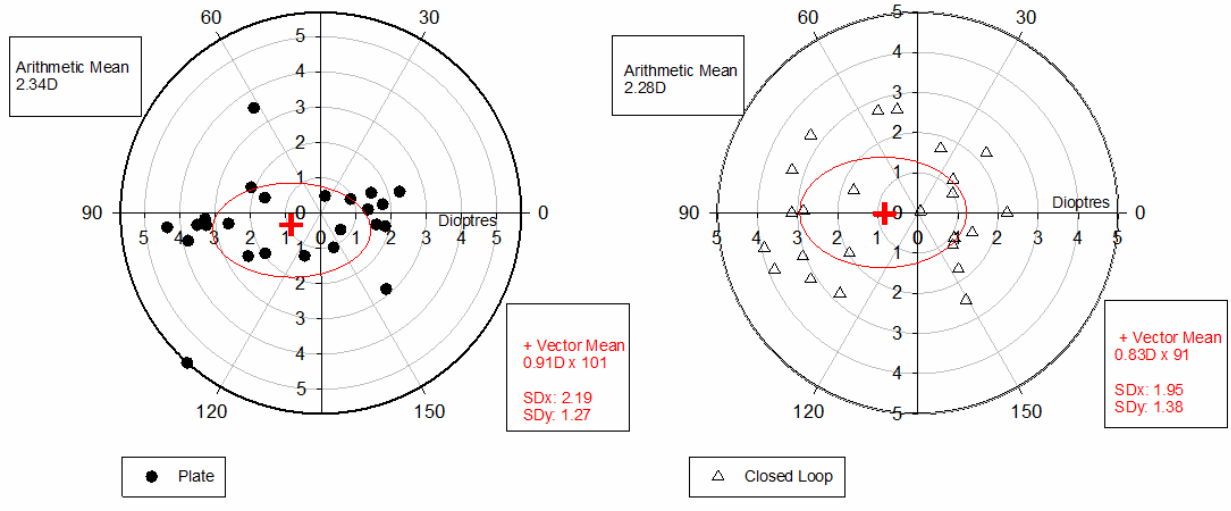


Figure 6.11: Visit 4 Surgically Induced Astigmatism

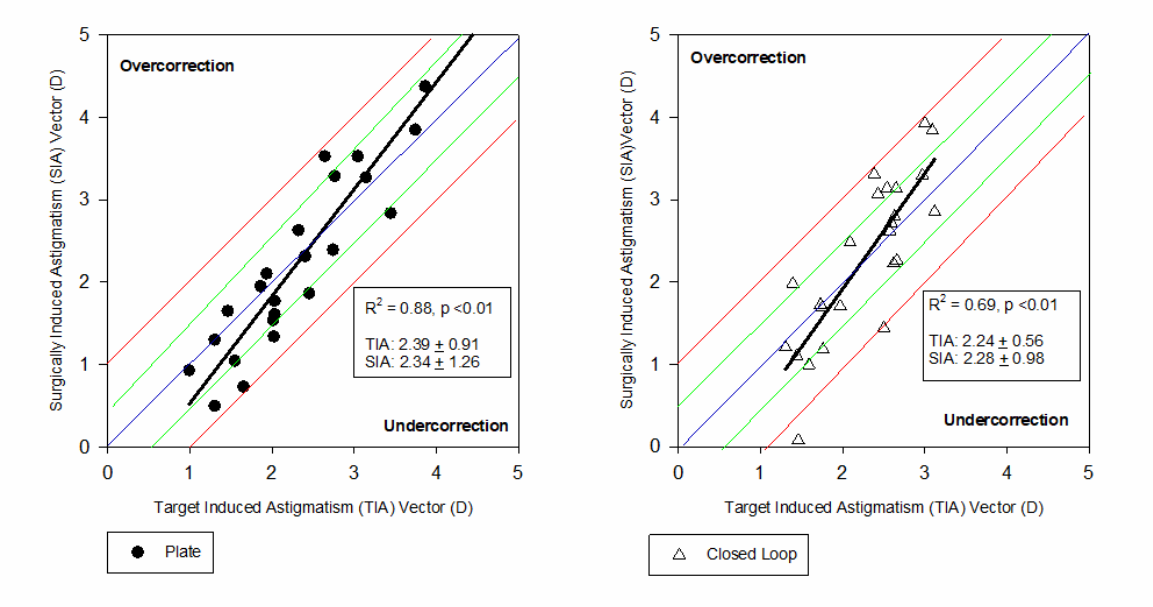


Figure 6.12: TIA vs SIA Visit 4

a) Closed Loop b) Plate

Absolute TIA and SIA were similar for both the plate haptic (p = 0.628) and closed loop haptic (p=0.859). In addition, there were good correlations between TIA and SIA in both closed Loop (R^2 = 0.69) and plate (R^2 = 0.86) haptic IOL groups.

6.6.7 Correction Index

The overall astigmatic correction was well targeted as demonstrated by the correction index (ratio of SIA to TIA) of 0.99±0.30 for the closed loop and 0.94±0.24 for the plate haptic IOLs (Figure 6.13). The eyes were then categorised as with-the-rule (within 30° of vertical), against-the-rule (within 30° of horizontal) or oblique. Interestingly, both groups demonstrated an undercorrection against-the-rule (ATR) astigmatism and an overcorrection for with-the-rule (WTR) astigmatism.

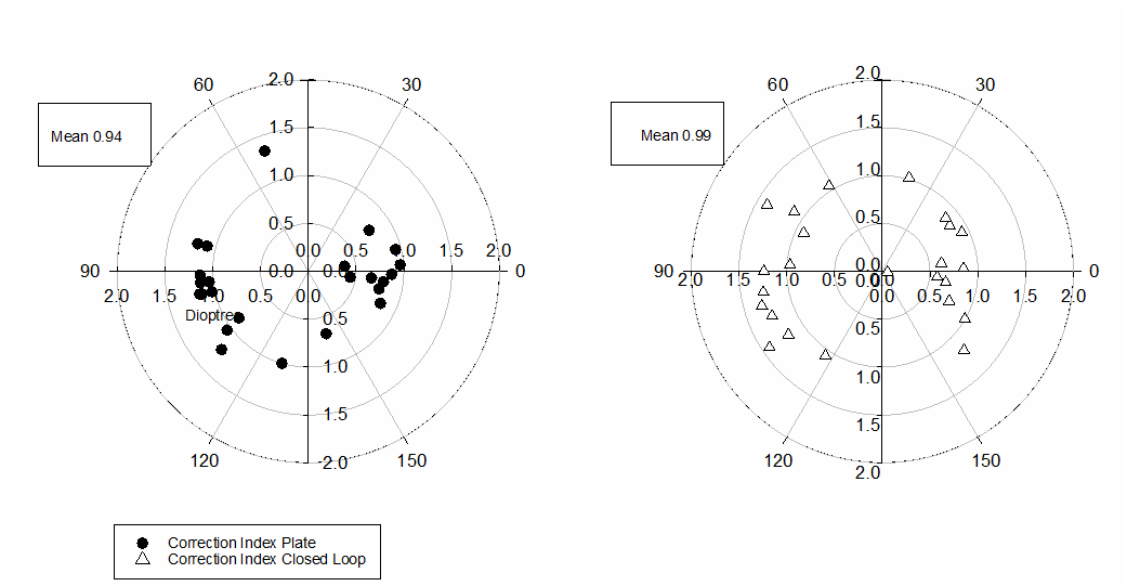


Figure 6.13: Correction Index

6.6.8 Difference Vector

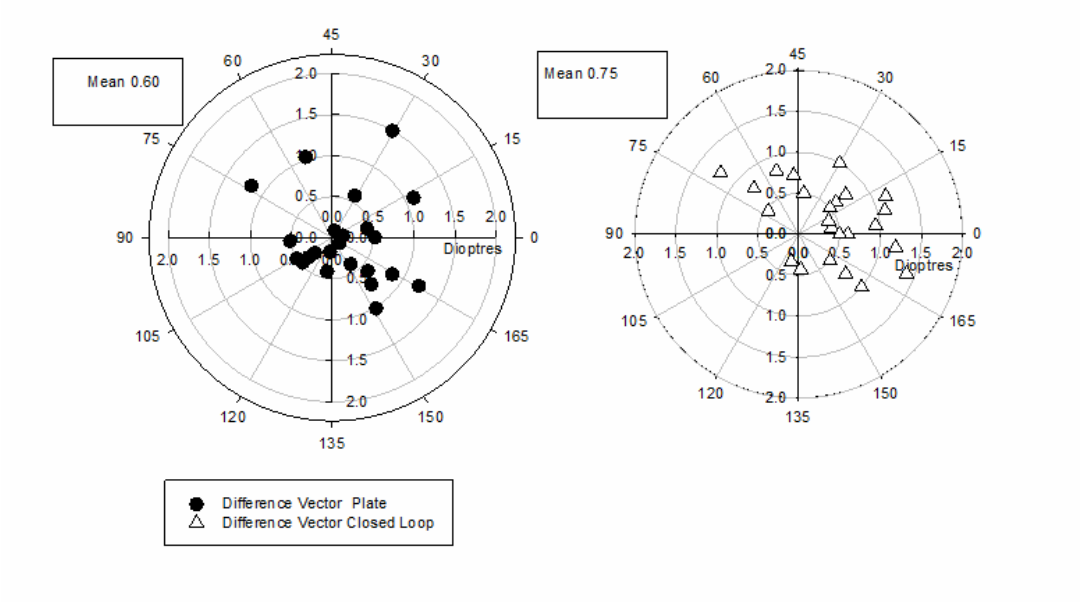


Figure 6.14: Difference Vector

The mean difference vector (difference between TIA and SIA), alternatively known as the error vector, was 0.60D in plate group and 0.75D in closed loop group, this was not a statistically

significant difference between groups(p = 0.131 and power 0.492)(**Figure 6.14**). The mean difference magnitude between groups was not statistically significant (p= 0.624) with a power of 0.663. When the groups were split into WTR, ATR and oblique astigmatism, the magnitude of error was examined and the undercorrection/overcorrection was further highlighted (**Figure 6.15**). It should be noted that there were very few subjects with oblique astigmatism in either group (plate n =3, closed loop n= 2). Neither the differences between groups for WTR (p = 0.160) nor ATR (p = 0.755) were statistically significant; *post hoc* testing of power was 0.518 and 0.765, respectively.

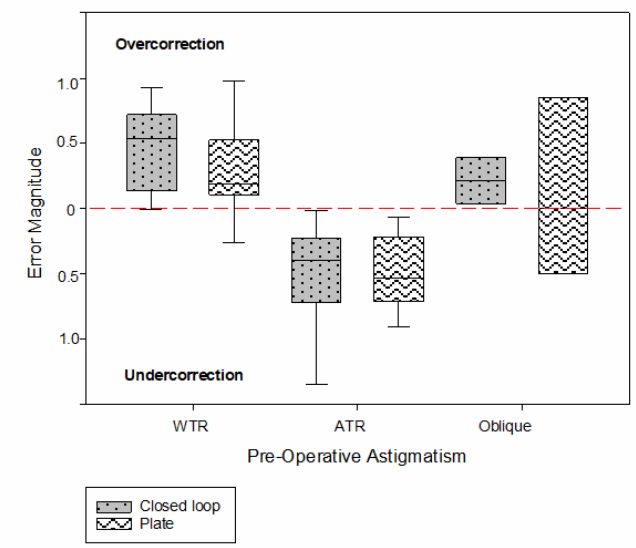


Figure 6.15: Difference magnitude. Error bars = standard deviation

6.6.9 Toric Calculators

The calculators provided by both Zeiss (plate) and Rayner (closed loop) have been updated since the operative stage of this trial. The pre-operative biometry data was entered in the new calculators, and new predicted residual refraction noted for those IOL powers implanted (**Figure 6.16**). From **Figure 6.16**, it can be seen that the new calculator for the plate haptic

resulted in an increased hyperopic difference, prediction shows slight myopia but refractive outcome is actually hyperopic.

Comparison of predicted residual spherical equivalent and actual showed significant differences in both groups, plate group p<0.01 and closed loop p = 0.04. Correlation was actually less in both instances than with the old calculators R = 0.315 plate and R = 0.230 Zeiss.

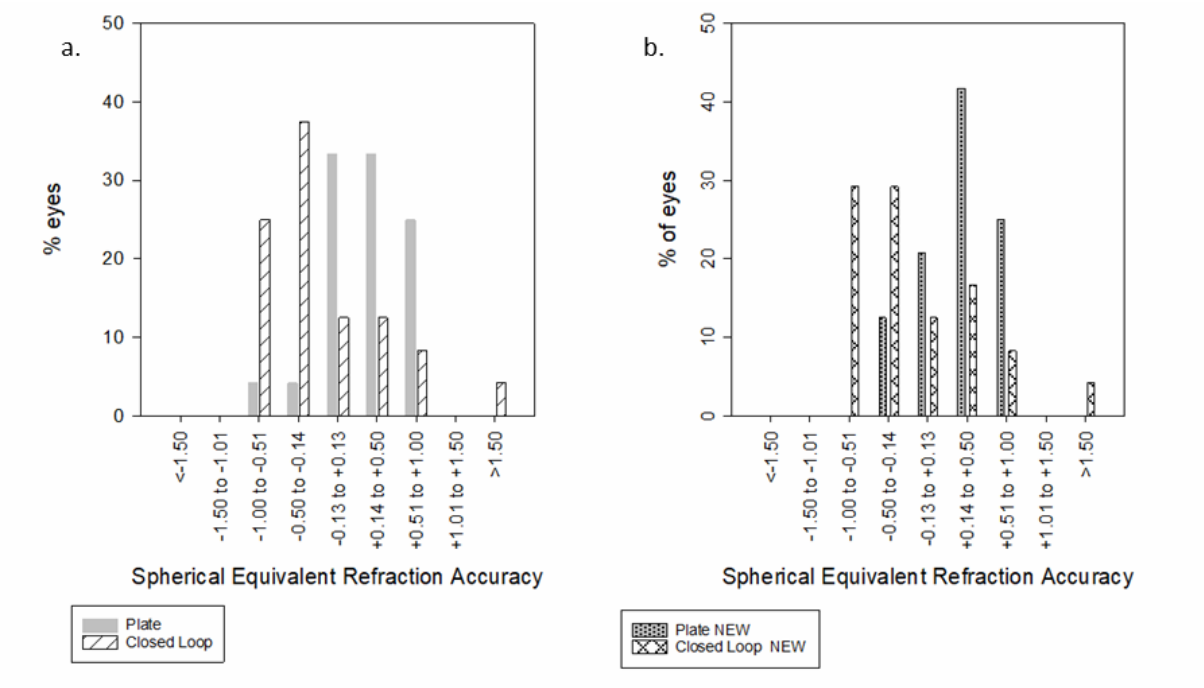


Figure 6.16: Comparison of Spherical Equivalent Refractive Accuracy

a. Orginal Calculator
b. New Calculator

6.6.9.1 Target Induced Astigmatism

Target Induced Astigmatism showed (Figure 6.17) no change to mean or standard deviation in the closed loop group (2.44 ± 0.56) , however there was a difference in the plate group, original calculator TIA= 2.37 ± 0.90, new calculator Mean TIA = 2.46 ± 1.03). This was not statistically

significant (Plate p = 0.421, power =0.44 Closed Loop p = 0.721, power = 0.568). Due to the small effect size <0.1 in both groups, a much larger sample size >3000 would be greater to realise a true Type II error statistically. As astigmatism can only be measured clinically in 0.25D steps then differences less than this are not clinically significant.

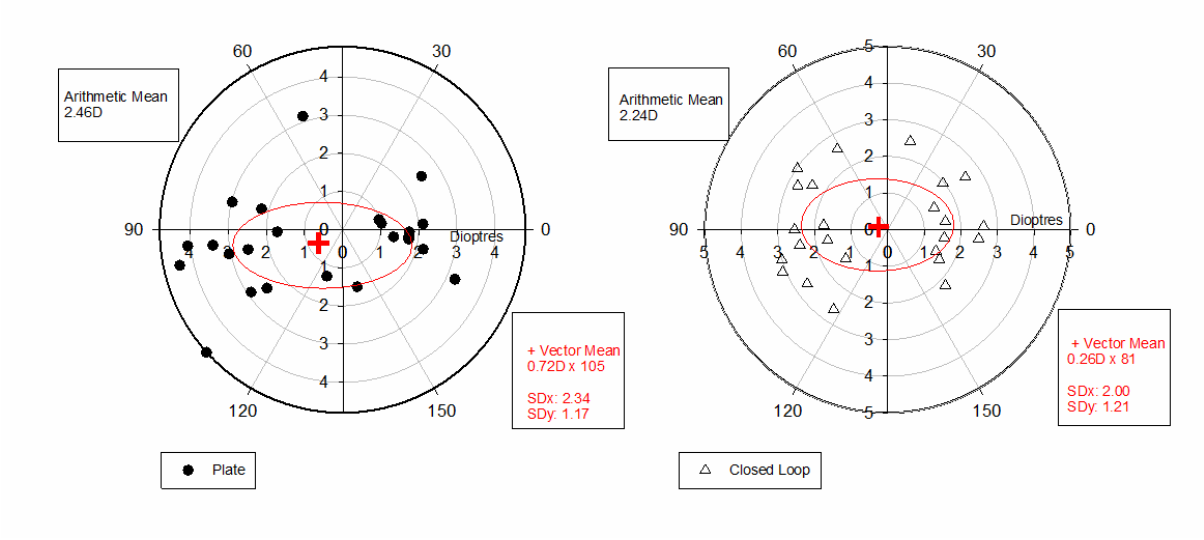


Figure 6.17: Target Induced Astigmatism with New Calculators

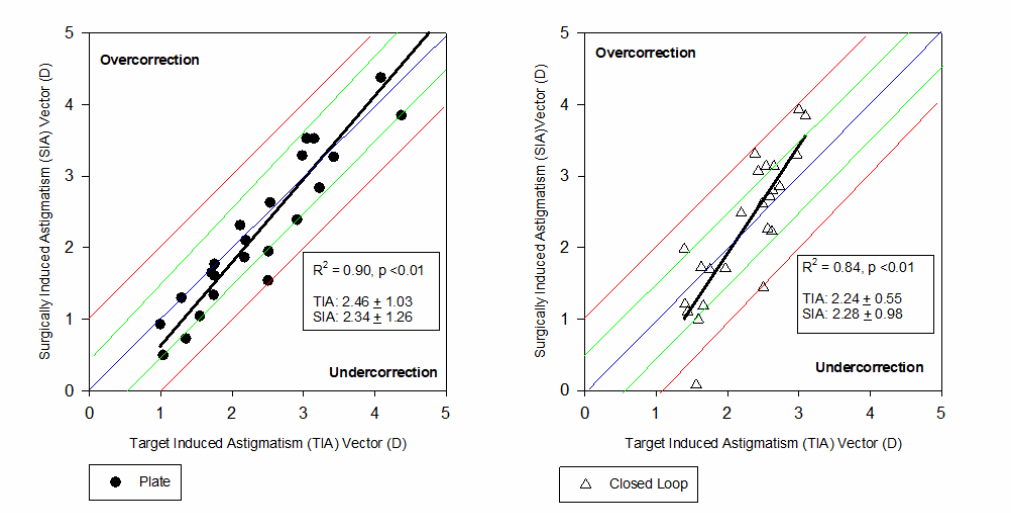


Figure 6.18: TIA vs SIA with New Calculations

The correlation between TIA and SIA was improved in both groups with the new calculators (**Figure 6.18**) (plate R^2 = 0.90 and closed loop R^2 = 0.84)

6.6.9.2 Correction Index

When the new calculators were used (**Figure 6.19 and Figure 6.20**), the mean correction index in the plate haptic actually reduced to 0.91±0.18, with no change in the closed loop group (0.99±0.30). Despite this, the difference in mean correction index between groups was not significant (p = 0.264). Also the plots highlight how the new calculator in the plate group has improved the CI in ATR astigmatism and reduced the over-correction in WTR astigmatism. There is very little difference in the closed loop group.

Table 6.8: Correction Index

Correction Index	Plate Old	Plate New	Closed Loop Old	Closed Loop New
Mean	0.94	0.91	0.99	0.99
Median	0.98	0.95	1.03	1.05
Min	0.38	0.48	0.05	0.05
Max	1.32	1.19	1.42	1.42

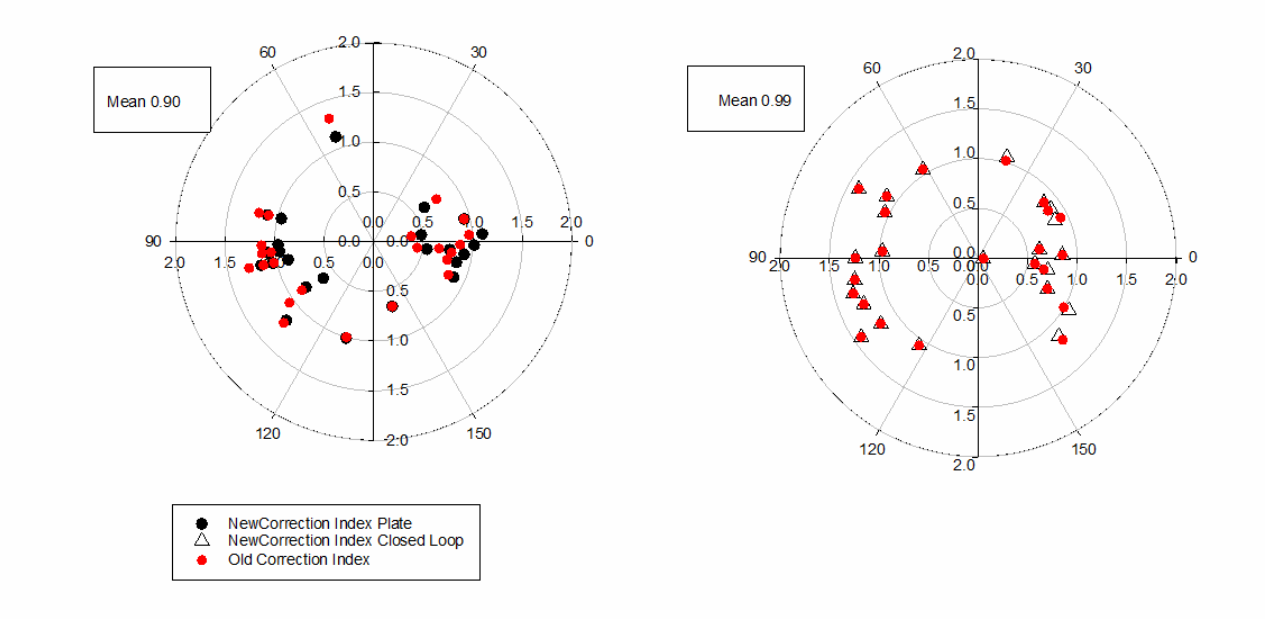


Figure 6.19: Correction Index with New calculator

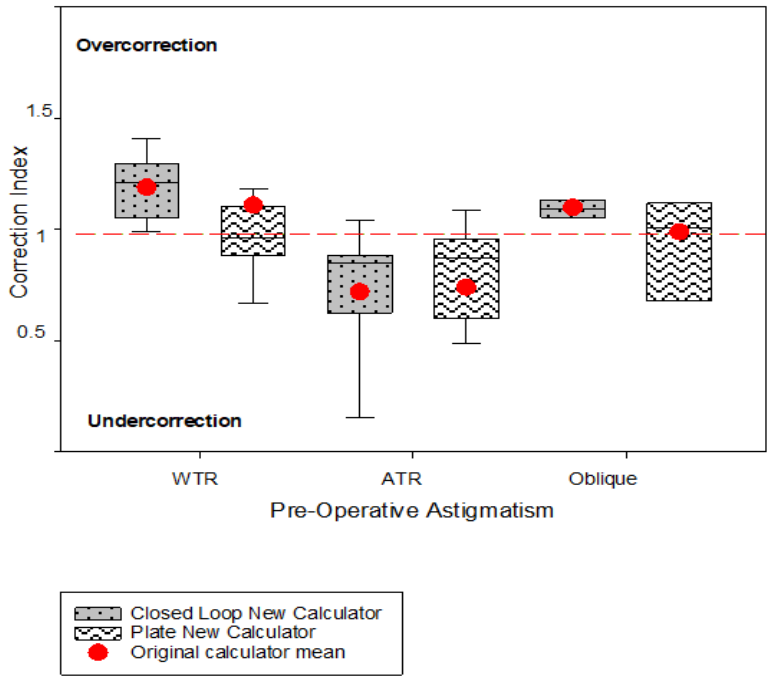


Figure 6.20: Comparison of Correction Index. Error bars = standard deviation

The difference vector was reduced in the plate group (0.57D) with the new calculator but not statistically significant (p = 0.658). There was no change in the closed loop group (0.75D).

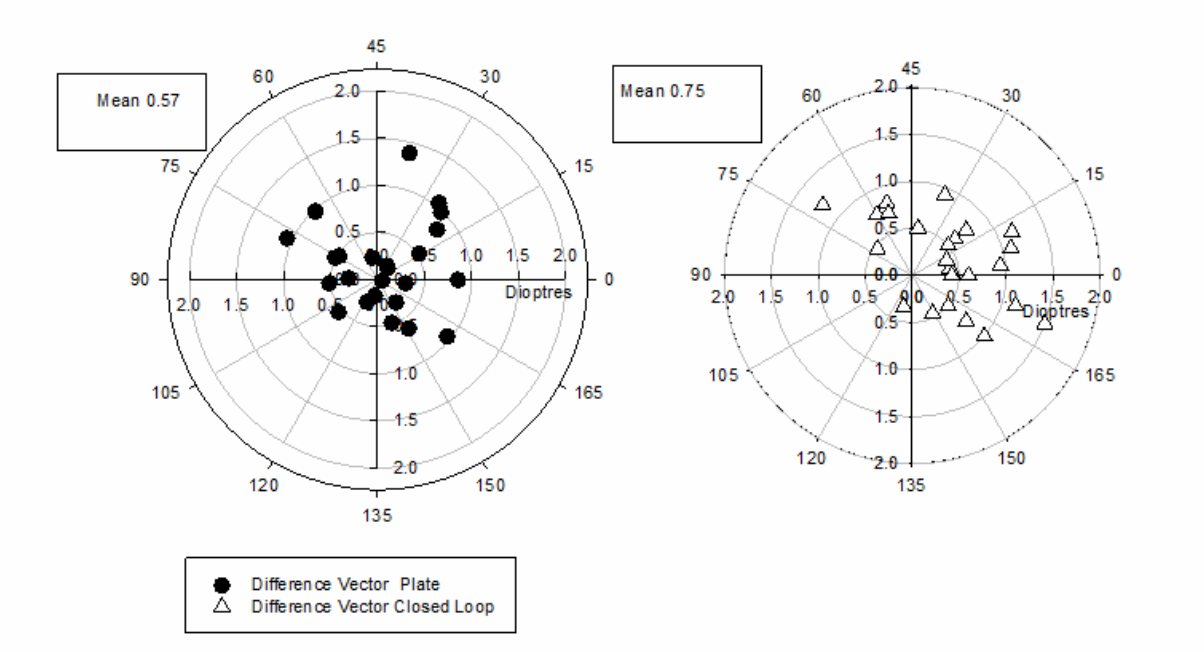


Figure 6.21*:* Difference Vector with new calculator

Using the new calculator showed a reduction in the error magnitude (Figure 6.22) for both with-the-rule (p = 0.090) and against-the-rule astigmatism (p = 0.238) in the plate haptic group, however it was not statistically significant. In the closed loop group there was no difference to the over correction of with the rule astigmatism (p = 1.00), but there was an improvement in the under-correction in the against-the-rule group (p = 0.80) although not significant. The oblique groups were too small to perform statistical analysis. The WTR (n =11) and ATR (n= 10) groups were also small and thus differences which may be significant in a larger sample size will not necessarily be evident.

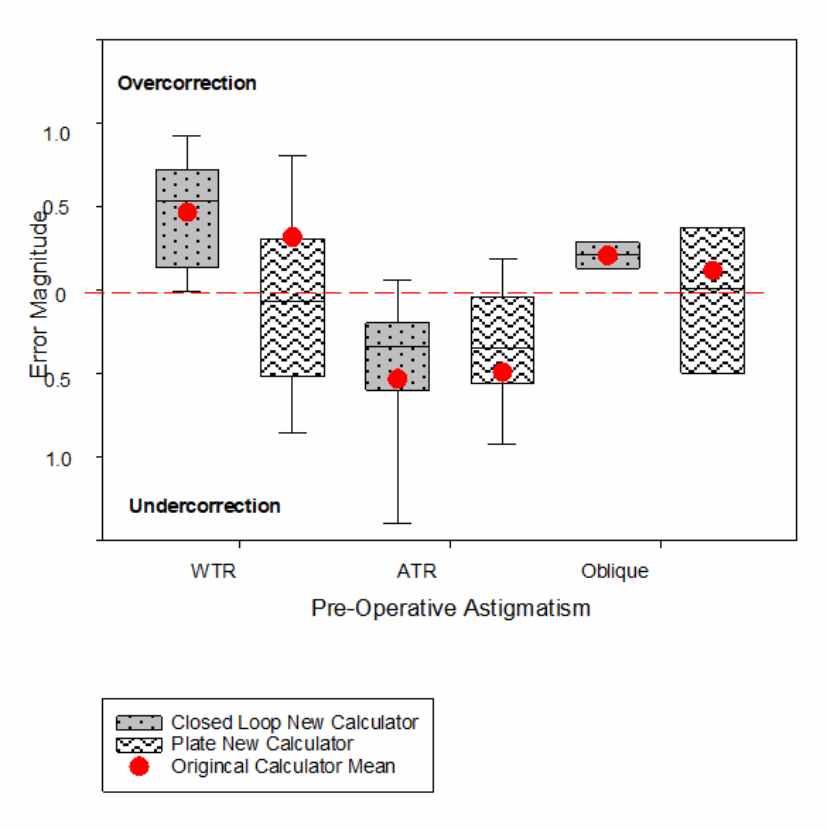


Figure 6.22: Difference magnitude with new calculator. Error bars = standard deviation

6.6.10 Rotational Analysis

Analysis of all images was performed by a single observer. In order to check the reliability of the images, a consistency angle was calculated by identifying the difference between the two sets of iris/conjunctival markings.

Immediately post-operatively, due to pupil dilation there was a loss of visible iris architecture or conjunctival congestion in some patients, and thus it was not possible to grade all images. Thus only 66% of images (34 of 52) immediately post-operatively were suitable for grading. However, 100% of images had sufficient clarity for grading at V1 and V2, 96% at V3 (50/52) and 98% (51/52) at V4.

Table 6.9 shows that the reliability of the measurements was approximately 2 degrees and as such,we can assume that the toric IOL axis can be reported confidently within 2-3 degrees; this was similar in both groups.

Table 6.9: Consistency Angle between visits			
Feature markings (°)	**Difference V1 to V2**	**Difference V2 to V3**	**Difference V3 to V4**
Plate	Mean 2.03 ± 2.06	Mean 2.28 ± 1.90	Mean 2.48 ± 2.92
	Median 1.69	Median 1.95	Median 1.83
Closed Loop	Mean 1.96 ± 1.70	Mean 1.74 ± 1.45	Mean 1.89 ± 1.51
	Median 1.61	Median 1.47	Median 1.55
Mean difference between feature markings ± Standard Deviation Median difference between feature markings Units = Degrees			

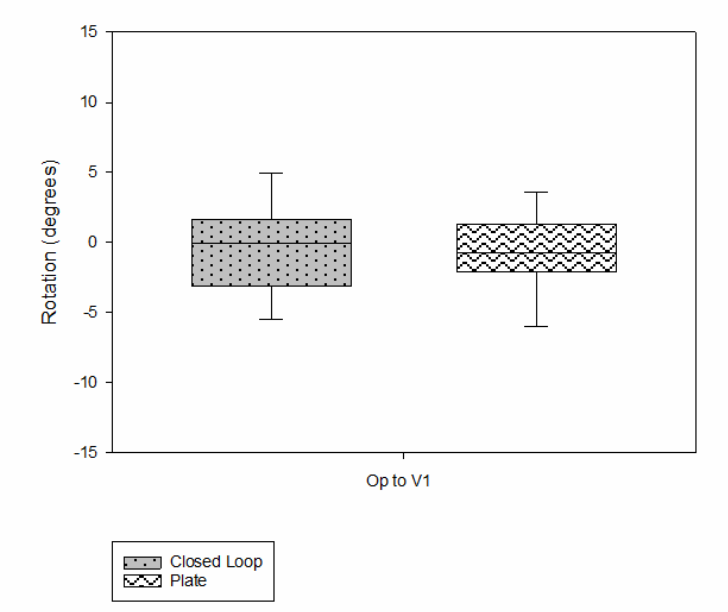


Figure 6.23*:* Early phase rotation (Op to V1). Error bars = standard deviation

In the early post-operative period (24-48hrs), absolute mean rotation in the Closed Loop group was 2.01° ± 2.29 and range from -8.15 to 5.48° and in the plate haptic group 3.24° ± 3.72 and range from -9.58 to 9.55 (**Figure 6.23**).

Table 6.10: IOL Axis Rotation from V1

Axis Rotation (°)	V1 to V2		V1 to V3		V1 to V4	
	Plate	Loop	Plate	Loop	Plate	Loop
Mean Rotation	2.40 ± 2.56	2.46 ± 1.80	2.45 ± 2.08	2.08 ± 1.49	3.08 ± 2.98	2.73 ± 1.91
Range	0.35 - 11.42	0.18 – 6.96	0.00 – 7.82	0.11 – 6.25	0.13 – 9.29	0.57 – 7.27
% rotated < 5°	84.6%	92.3%	84.6%	92.3%	80.8%	88.0%
% rotated < 1o°	96.2%	100%	100%	100%	100%	100%

Absolute Mean rotation ± Standard Deviation
Range °
Units = Degrees

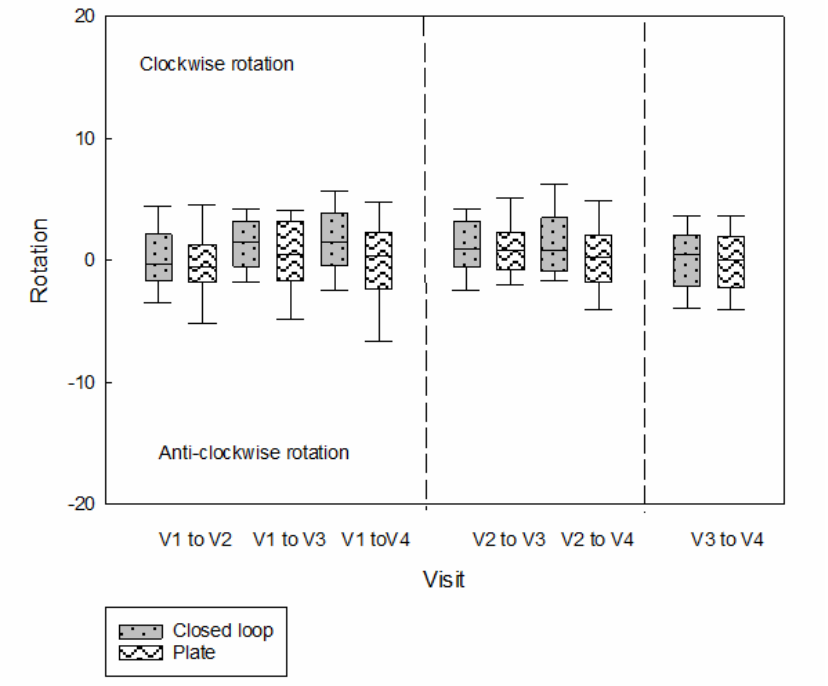


Figure 6.24*:* Rotation between visits. Error bars = standard deviation

There was no significant difference in rotation within each group from visit to visit (Plate F_5 = 0.827, p = 0.533, power = 0.60) Closed Loop (F_5 = 0.09, p = 0.924, power = 0.94), nor was there any significant difference between groups ($F_{1,5}$ = 0.606, p = 0.447)(**Table 6.10, Figure 6.24**).

6.6.11 Surgical re-intervention for rotation

Four subjects (referred to as subjects A-D) (2 closed loop, 2 plate) underwent surgical rotation of their TIOL within 2 weeks of their original surgery, their results prior to realignment were excluded all previous analysis. Subject A, anti-clockwise rotation of >15° was noted during post-operative slit lamp photography and the patient was taken back to theatre on the same day. However, when she attended for V1, 24 hours later, again similar rotation was noted and subject declined further intervention. In all other subjects, rotation was noted at V1 (24 hours post-operatively).

Table 6.11: Rotation requiring surgical intervention

	Subject	Intended Axis	Pre-intervention rotation	Post-intervention rotation	Direction of rotation
Closed Loop	A*	65	18.62	19.26	Anti-clockwise
	B	119	30.95	1.17	Anti-clockwise
Plate	C	91	22.85	3.30	Clockwise
	D	80	13.78	3.95	Anti-Clockwise

Unit = degrees
*subject declined second intervention

Following intervention, the remaining 3 subjects had improved outcomes and remained stable for the rest of the study visits (Table 6.12).

Table 6.12: Surgically induced astigmatism

	Subject	Pre-intervention			Post-intervention		
		UDVA	CDVA	SIA	UDVA	CDVA	SIA
Closed Loop	A*	N/A			0.40	0.10	2.19
	B	0.50	0.34	4.62	0.10	0.04	4.20
Plate	C	0.28	0.06	2.57	0.00	0.00	2.72
	D	0.36	0.20	4.99	0.20	0.10	3.71

Units, UDVA, CDVA =LogMAR, SIA= dioptres
*subject declined second intervention

From Table 6.11, it is clear that the TIOLs were implanted close to the vertical meridian in all subjects (with the rule astigmatism).

6.7 Discussion

The results highlight that implantation with both a closed loop and plate haptic toric intraocular lens delivers accurate astigmatic correction as demonstrated by an average correction index of 0.99 and 0.94. Visual acuity testing found that UDVA was 0.20LogMAR or better in 92% of the closed loop group and 88% of the plate haptic group by 3 months (V4) and CDVA was 0.10LogMAR or better in 96% of the closed loop group and 100% of the plate haptic group. These results were similar or better to previous studies investigating these particular lenses (Alberdi et al., 2012, Bascaran et al., 2013, Seth et al., 2018). When split into WTR and ATR astigmatism it was clear that a marked over correction occurred when correcting WTR and undercorrection occurred with ATR astigmatism. This finding was demonstrated by Koch who proposed that the posterior corneal surface is toric in nature and suggested the use of the

nomogram where it was not possible to assess the posterior corneal surface (Koch et al., 2013). Since the operative stage of this trial, both toric calculators were updated and hence we assessed the accuracy using the results from these calculators. The Zeiss updates demonstrated the greatest change; significantly reducing the overcorrection when WTR and the undercorrection in ATR. Toric IOL calculation is evolving with the science and is iteratively improving the accuracy of results. Prior to using a proposed nomogram, it is vital to determine if updates to a toric calculator have been applied that incorporate a compensation for the posterior corneal surface (Abulafia et al., 2015, Abulafia et al., 2016, Ferreira et al., 2017b, Ribeiro et al., 2019).

Significant differences were found between predicted spherical equivalent and actual spherical equivalent in both groups, however when measuring actual post-operative refractive error it is only possible to the nearest 0.25D, and the calculators are not constrained by such step sizes.

Previous studies have shown good rotational stability, 86% rotated < 10° in plate haptic (Bascaran et al., 2013) and 92.6% < 10° in closed loop haptic (Alberdi et al., 2012). Seth (Seth et al., 2018), also assessed rotational stability in the AT TORBI 709 plate haptic and had rotation of < 10° in 95.2% of subjects, however no secondary interventions occurred. In the present study, four subjects had a rotation greater than 10° within the first 24 hours and underwent further surgical re-alignment within 2 weeks of the original surgery translating to a secondary intervention rate of around 7% for both lenses. This is a higher rate than previously demonstrated (Chang, 2008, Miyake et al., 2014, Oshika et al., 2018, Waltz et al., 2015). This may be explained by the variance between practices as different surgeons will consider surgical re-alignment at differing levels of misalignment, depending on visual acuity and patient choice In the current study, repositioning occurred with a strict conservative criteria of a misalignment >10°.

Previous reports (Miyake et al., 2014) suggest that toric IOL rotation occurred mostly within the first week post-operatively and our study concurred with all rotation >10° occurring within the first 24 hours and no significant differences were found in rotation from V1 onwards. Previous literature proposed that IOL rotation was most likely in longer axial lengths and lowered powered (thinner) TIOLs (Lee and Chang, 2018, Miyake et al., 2014). In our sub-set all had AL >25mm and TIOL powers were ≤12D, thus supporting his conclusions (Miyake et al., 2014). Our subset, also, all had WTR astigmatism and a previous study suggested that the incidence of rotation was greatest when there was a vertical axis of implantation (Ruhswurm et al., 2000).

No significant differences were found between the groups in terms of rotational stability. Our mean rotation at 3 months was 3.08° ± 2.98 plate haptic and 2.73° ± 1.91 in the closed loop group. This was also similar to rotation reported in the literature with other commonly used TIOLs (Chang, 2008, Lee and Chang, 2018, Miyake et al., 2014).

Previous literature has described early rotation to be more likely in plate haptics than loop haptics, although this was not supported in Bascaran's study of the AT TORBI plate haptic (Bascaran et al., 2013, Chang, 2008). The literature demonstrates excellent long-term stability in plate haptic TIOLs as they are less susceptible to compression forces in capsular contraction (Patel et al., 1999). Plate haptics have positioning holes which allow for easier manoeuvring during implantation. These holes also allow lens epithelial cells to migrate and can anchor the lens in place (Mamalis et al., 1996) thus maintaining rotational stability. Late rotation is believed to be more likely in open loop haptics due to the compressive forces of capsular bag contraction. However, previous studies have utilised TIOLs of not only different haptic design but also different IOL materials and it is known that increased friction between the IOL and capsular bag, in acrylic lenses compared to silicone lenses increases stability

(Chang, 2008, Oshika et al., 1998). The effect of such compressive forces is believed to be reduced in closed loop haptics as the outer haptic closes against the inner haptic and thus locks the lens in place, improving stability.

Differences in rotational stability between visits was not apparent in this study and no conclusions could be drawn regarding early and late phase rotation. Both TIOLs showed good stability. Inoue (Inoue et al., 2017) assessed axis misalignment within 1 hour of surgery and found approximately 2° of rotation was actually the result of poor alignment during surgery. This was not accounted for in this study due to the difficulties in imaging immediately post-operatively, dilution of pre-operative markings, conjunctival injection and marked dilated pupil or marked pupil constriction in the immediate post-operative period, all contributed to difficulty in imaging the IOL markings accurately and identifying conjunctival or iris landmarks to compensate for head rotation. Operative misalignment must be considered a contributing factor to apparent rotation, although manual marking techniques have been reported to be accurate (Bayramlar et al., 2017), more recent advances in digital alignment surgical systems are reported to further improve reliability and reduce misalignment errors (Lipsky and Barrett, 2019, Mayer et al., 2017).

Not only immediately post-operatively but at all visits, precise analysis of IOL rotation remains challenging, as accuracy of measurement is multifactorial depending on image quality, adequate pupil dilation, ability to detect sufficient iris/conjunctival features and observer reliability. A multi-centre study highlighted the variation in image quality between sites and reported that poorer image quality was related to increases in apparent rotation (Wolffsohn and Buckhurst, 2010). All images in this study were analysed by the same masked clinician, and consistency angle between 2 sets of reference markings was within 2° at each visit, this allowed compensation for head rotation, however further analysis by a second masked observer would enhance determination of image accuracy.

6.8 Limitations

This study is limited by various factors. Although the post-operative visits were carried out by a masked observer, it was obvious, once the patient was dilated which IOL had been implanted. Thus, for future studies, it may be more appropriate to have a masked observer for refractive measures and an unmasked observer for clinical photography/rotational analysis. Ideally, rotational analysis would be validated by a second observer also. Image quality limits rotational analysis also. A dilated pupil is required to assess the TIOL markings, however some iris features are lost depending on the extent of dilation achieved. Also the use of Phenylephrine as a mydriatic, aided in achieving adequate pupil dilation, however its vasoconstrictive properties change the appearance of conjunctival vessels which could otherwise by used as distinct markers to assess rotational stability.

Posterior corneal astigmatism was not measured directly nor did we employ a nomogram to account for this. We relied entirely on the manufacturers calculators to establish refractive predictions.

6.9 Conclusion

In conclusion, both the Zeiss AT TORBI 709M plate TIOL and the Rayner T *flex* 623T closed loop TIOL show excellent rotational stability and refractive outcomes, however further improvements in toric IOL calculations/digital alignment systems may improve outcomes further.

In summary, the primary findings of this study are:

- No significant differences in rotational stability were found between haptic designs

- In both TIOLs there was an overcorrection of WTR astigmatism and undercorrection of ATR astigmatism
- In both TIOLs, the updated manufacturers calculator improved the undercorrection of ATR astigmatism

6.10 Supporting Publication

This chapter forms the basis of the research paper:

Law, E.M., Aggarwal, R.K., Buckhurst, H., Kasaby, H.E., Marsden, J., Shum, G. and Buckhurst, P.J. **A randomised intra-patient comparison of closed loop and plate haptic toric intraocular lenses in patients with bilateral astigmatism**. *J Refract Surg*. Under Review

Chapter *7*

Summary and Conclusion

7.1 Introduction

With a plethora of multifocal and toric intraocular lenses now widely accessible to surgeons, spectacle independence for many patients is an achievable notion. Advances in IOL design and in ocular biometric formulae have significantly improved post-operative outcomes, yet there remain inherent issues when calculating MIOL and TIOL powers. In addition, the choice of MIOL is of upmost importance and can be tailored toward the patient's lifestyle. In order to do so, clinicians must fully understand the functionality, advantages and disadvantages of MIOL designs, enabling them to appropriately counsel the patient pre- and post-operatively and provide a personalised medicine approach to each individual.

7.2 Curve fitting techniques to enable analysis of defocus curves

Defocus curves are used frequently in MIOL studies but there is a lack of consistency in the methods of analysis. This leads to an inability to directly compare data from one study to another and limits the usefulness of the data reported. In Chapter 2, the benefits of the range of focus and area of focus methods of analysis were discussed (Gupta et al., 2008, Buckhurst et al., 2012b), yet they are not widely used in the literature. This may be due to the need to fit a polynomial curve to the data, the mathematical derivation required to record the RoF and

AoF metrics or indeed ambiguity on how to statistically assess the validity of curve fitting (goodness of fit). Chapters 3 to 5 are dependent on an accurate fitting profile for both the assessment of addition power and the evaluation of visual function and hence it is critical that the most valid approach to curve fitting can be established. In light of this, the study explored the curve fitting method, with the aim of determining the best method to fit curves to defocus data and thus standardise and simplify the methodology for future research. Unfortunately, a clear method of polynomial fit could not be conclusively established that was robust for all of the IOLs we studied. Some statistical methods (AICc and Snedecor&Cochrane) were simply too conservative and as such under-fitted the data resulting in the loss of the near inflection point. However, fitting of a cubic spline was found to be effective in all IOLs, hence this method is used for defocus analysis in Chapters 3, 4 and 5 thereafter. The use of piecewise polynomials in a spline curve guards against over-fitting or under-fitting (Bartels, 1998). This advocates the use of spline curves in defocus analysis. However, complex mathematical modelling is required to derive the desired DoF and AoF metrics and this may pose a challenge. If it is not possible to use spline curves, then the results in Chapter 2 suggest the adjusted R^2 method is the most appropriate method of establishing goodness of fit, but it should be used with caution and visual inspection as an additional process may further guard against over and under-fitting of the data.

7.3 Predicting the post-operative addition power of an MIOL

Defocus profiles give important information regarding the near addition power of an MIOL, a factor which again should be tailored towards patients' needs and lifestyle. Despite the fact that addition power at the spectacle plane provides a better reflection of the actual near

working distance provided by a multifocal intraocular lens (MIOL), manufacturers do not offer this information and instead only describe near addition power at the IOL plane. The addition power can be defined as the dioptric distance between peaks in the curve. Using the curve fitting methodology advocated in Chapter 2, Chapter 3 sought to further investigate reading addition. Previous literature described in Chapter 3, has shown that addition power will vary dependent on an individual's ocular biometric measures thus this study aimed to investigate the prediction of the post-operative addition power at the spectacle plane and proposed a novel simple method that can be easily utilized by clinicians to predict effective addition power. The effective addition power achieved post-operatively was taken as the dioptric distance between the near and distance inflection points of the defocus curve. A variation of 1.14D between subjects was found, thus a large enough variation to expect a clinical difference in near performance to be apparent. Five commonly used formulae were used to predict post-operative addition power. The SRK/t, Holladay and Hill RBF all tended to underestimate addition power. The Haigis formulae produced similar means, yet had significant proportional bias. However, the Barrett formula showed similar means, the highest correlation and also the lowest proportional bias when compared to the effective addition power, thus we concluded our simple method of predicting addition power was most effective when using the Barrett formula, thus enabling clinicians to tailor add power to a patient needs, and perhaps, more importantly, it could be used to check pre-operatively to ensure that an individual's ocular biometry will not result in an aberrant addition power.

7.4 Comparison of visual function and patient satisfaction following bilateral implantation of monofocal and bifocal intraocular lenses

Previous Cochrane reviews, (Calladine et al., 2012, de Silva et al., 2016, Leyland and Pringle, 2006) outlined in Chapter 1, highlighted the need for robust randomised control trials of multifocal IOLs and a standardisation of methods utilised. As such, this study, met those requirements and proposes a robust methodology with the aim of establishing standardisation for future studies. The methodology was designed with rigour at the forefront, utilising more than one method for each metric. Patient reported outcomes were also included in order to assess satisfaction. The study assessed an MIOL design with a lack or prior studies and as such was in need of evaluation. Near vision was significantly improved in the MIOL group as assessed using clinical measures, including the near AoF defocus metric, and patient satisfaction for near tasks was greater in the MIOL group. No differences were found with distance or intermediate visual acuity, yet patient satisfaction was greater for intermediate (computer) tasks in the MIOL group. Intermediate vision is not a clearly defined metric, in this study a testing distance of 70cm was used, however not all studies agree. The bifocality of this MIOL would indicate optimum performance at distance and near, yet satisfaction was greater compared to the monofocal even at intermediate, suggesting that the increased range of focus achieved with a bifocal enhances intermediate somewhat. Spectacle independence was relatively low in this study when compared to the majority of MIOL studies (Baig et al., 2016, Cillino et al., 2008, Cochener et al., 2009, Mendicute et al., 2016). This can be attributed to the relatively atypical cohort for MIOL implantation which represented a relatively older cohort for which independence was not the motivating factor. Age is an important factor for MIOL implantation as an older eye has a smaller and less mobile pupil (Fotiou et al., 2007, Winn et al., 1994). Given that the light distribution profile of a MIOL is dependent on pupil size it is important to assess

visual function in a variety of age groups. It is reasonable to assume that subjects willing to participate in a randomised trial are thus indifferent to the prospect of spectacle independence. Furthermore, if spectacle independence is not a motivating factor, then such subjects may resort to spectacles post-operatively for even minor refractive error or minimal gain in VA. In contrast, in cohort studies, spectacle independence is likely to be a significant motivating factor, and subjects will be less keen post-operatively to return to spectacles.

Our suggested protocol for MIOL studies includes distance, intermediate and near VA using LogMAR charts, defocus profile, using Gupta's (Gupta et al., 2007) method of data collection, the curve fitting method outlined in Chapter 2 and Buckhurst's (Buckhurst et al., 2012b) area of focus metric. Contrast sensitivity, Dysphotopsia and patient reported outcomes including spectacle independence should all be assessed when evaluating MIOLs also. This suggested protocol is broadly in agreement with recently published recommendations (Evans et al., 2020).

7.5 Comparison of visual function and patient satisfaction following bilateral implantation of trifocal and extended depth of focus intraocular lenses

Chapter 5 compares two cohorts, a trifocal group and an extended depth of focus group. Although previously cohort studies had been published comparing these two IOLs, this was the first study to assess one year post implantation. These subjects were assessed using the same protocol as Chapter 4 and curve fitting technique proposed in Chapter 2. Excellent distance and intermediate VA was achieved in both groups. However, the AoF metric highlighted the EDoF group to have a larger range of intermediate vision, yet this was not evidenced in patient

reported outcomes. Near Acuity, Radner reading performance and spectacle independence was significantly better in the trifocal group. No differences were found in contrast sensitivity between groups. Halos and glare were reported in both groups, simulator scores were significantly larger in the trifocal group at the 3-6 month visit yet there was no difference in patient satisfaction scores relating to dysphotopsia thus it is assumed that the difference in physical appearance of the halos is not sufficient to be clinically detrimental. This also confirms the need for questionnaire style analysis of dysphotopsia, as the simulator scores only would lead to the assumption of an inferior result with the trifocal. There was no significant difference in halo simulator scores by the one year post-operative visit suggestive of neural adaptation. Despite the three focal points of the trifocal splitting the light distribution compared to the EDoF, there is no clinically significant inferiority of the trifocal, thus for most subjects there would be no advantage in choosing an EDoF IOL as opposed to a trifocal. However, despite the lack of near vision with the EDoF, complete spectacle independence was still achieved in 50% of subjects, thus adequate range was achieved for some lifestyles.

7.6 Intra-patient comparison of closed loop and plate haptic toric intraocular lenses

Not only does presbyopia result in spectacle dependence post cataract surgery, uncorrected astigmatism can also be detrimental to visual outcomes. The use of toric lenses can improve outcomes and increase the likelihood of spectacle independence. Chapter 6 investigates two differing TIOL designs in terms of rotational stability and refractive outcomes. The TIOLs had similar rotational stability, a small subset of patients had excess early phase rotation but this was in keeping with previous reports where rotation is expected to be greater in subjects with

longer axial lengths and requiring vertical alignment (Lee and Chang, 2018, Miyake et al., 2014). Visual outcomes were also good, yet an over-correction if WTR astigmatism and an under-correction of ATR astigmatism was seen in both groups. This is a known issue with toric IOL calculators, thus we investigated both manufacturer's updated calculators retrospectively and improvements were noted with the Zeiss calculator in both WTR and ATR, but only with WTR in the Rayner cohort, suggesting that further improvements are still required.

7.7 Discussion

Spectacle independence is one of many factors to consider when adopting a personalised medicine approach. However, known disadvantages of MIOLs such as dysphotopsia must also be addressed (Woodward et al., 2009).

As yet, there are no IOLs that can restore the natural accommodative function of the young phakic eye. Thus, in order to manage expectations and provide a realistic portrayal of likely post-operative visual function for presbyopic corrections, clinicians require in-depth knowledge of available MIOLs and their functionality. However, previous reviews have highlighted the need for standardisation in MIOL studies (Calladine et al., 2012, de Silva et al., 2016). This thesis proposed a methodology to ensure standardisation and provide a comprehensive assessment of IOLs. From the results of Chapter 4 and Chapter 5 where a monofocal, bifocal, trifocal and EDoF IOL were assessed, it is apparent that the methodology is sufficient to differentiate between the IOL types. Evans (Evans et al., 2020) recently proposed a minimum set of outcome measures for MIOL studies, including distance and near acuity using LogMAR charts, contrast sensitivity using the Pelli-Robson test and dysphotopsia, quality of life and spectacle independence via a questionnaire. The method used in this thesis

(Chapter 4 and 5) includes all of their suggested measures, however we have also considered reading performance using the Radner charts and defocus profiles. Rosen (Rosen et al., 2016) has also previously advocated for the use of defocus profiles in MIOLs studies. Chapter 5 also highlighted their importance as simple VA testing at 70cm found no differences between EDoF and trifocal for intermediate vision, yet defocus analysis using Buckhurst's Area of Focus metric (Buckhurst et al., 2012b) shows a superiority of the EDoF when an intermediate range is considered (50cms to 2m). Similarly, although Chapter 4 found no difference in distance acuity (corrected or uncorrected), there was superiority of the monofocal IOL when distance area of focus was considered at the 3 months post-operative visit. The use of Buckhurst's area of focus metric, provides a global overview of an IOLs performance throughout the visual range and avoids inadvertent bias resulting from choice of a single working distance for intermediate or near testing. Previous Cochrane reviews have remarked on the inconsistencies of near vision testing (Calladine et al., 2012, Leyland and Pringle, 2006). Intermediate vision is relatively difficult to define, often it is considered as the vision required to use a computer or read music, yet that can vary considerably, for example, between a laptop and a desktop computer user. Rosenfield suggest that although 50-100cm was historically considered computer viewing distance, with the advent of smaller screens and portable devices this was now often 30 to 60cms (Rosenfield, 2011). Despite the similarity found in intermediate vision in Chapter 4 between the monofocal and bifocal at 70cms or in the intermediate area of focus, the monofocal subjects reported greater levels of difficulty with computer use than those with MIOLs. Conversely, although superior intermediate area of focus was found in the EDoF group compared to the trifocal, no differences were reported in difficulty using a computer. Thus, the assumption of intermediate vision as best suited to computer use, may be an oversimplification. Additionally, these contradictory findings not only highlight the importance of considering visual function in ranges of working distances rather than at arbitrary testing

distances, but also reinforce the importance of patient reported outcomes and personalised medicine, ensuring choice of IOL to best suit a patient's individual needs and working distances. We postulated in Chapter 1, that the lack of uptake for the area of focus method, could be due to difficulties incurred with the necessary curve fitting, and perhaps a lack of understanding of curve fitting methodology in the ophthalmology community. Therefore, the exploratory study in Chapter 2 provides the guidance that was previously lacking and established that the use of a cubic spline is appropriate for a range of EDoF and MIOLs. This contribution, when applied to Buckhurst's (Buckhurst et al., 2012b) analysis metric, and in conjunction with Gupta's (Gupta et al., 2007, Gupta et al., 2008) methods for standardised collection of defocus data, should ensure that reliable and meaningful comparison of defocus data between studies is now achievable.

In addition, the fitting of a cubic spline to defocus data, allowed us to accurately establish the post-operative addition power of a MIOL at the spectacle plane. Based on this data, Chapter 3 established a novel and simple method for predicting addition power using the Barrett II Universal IOL formulae. This prediction will highlight possible aberrant results and allow further optimisation of MIOL choice by ensuring the effective addition likely to be achieved is appropriate for the individual's needs. This includes the choice of reading addition to achieve the desired post-operative reading distance most suited to a patient, and this can now be predicted using the simple clinical method established in Chapter 3.

The duration of follow up is also an important consideration due to the possibility of neuroadaptation (Rosa et al., 2017b, Mukai et al., 2007) and since our studies commenced, further literature has been published which suggested that longer term follow up (6-18 months) should be used when assessing MIOLs (Evans et al., 2020, Rosen et al., 2016, Wang et al., 2017). Thus supporting our decision to include a 12 month follow up interval in our MIOL

studies. Rosa showed that the cortical processing necessary in MIOL subjects reduced after 6 months post-operative interval (Rosa et al., 2017a). Both Chapter 4 and 5 subjects saw improvements in contrast sensitivity at the 12 month post-operative interval compared to 3 months. Also there were improvements in glare scores and reading performance with our MIOL subjects, although these improvements were not always statistically significant between visits. Similar improvements to contrast sensitivity, reading performance and also dysphotopsia have also been reported in previous literature (Anton et al., 2014, Goes, 2008, Kohnen et al., 2009, Montes-Mico and Alio, 2003, Sood and Woodward, 2011).

There is higher agreement in the methods of assessing TIOLs in previously published literature, yet not all TIOL designs have been compared and contrasted, this thesis sought to compare two TIOL designs in a randomised control trial. An intra-patient format was used as it is known that rotation can occur due to capsular bag size and contraction, and that the capsular bag varies between individuals (Glasser, 2008). In addition, individual TIOL manufacturers provide their own TIOL calculators for use with their lenses and we compared the refractive predictability between manufacturers and also intra-manufacturer by retrospectively assessing updated versions of their calculators.

7.8 Limitations

There are a number of limitations in the studies included in this thesis

7.8.1 Defocus Analysis

Defocus analysis is fundamentally important to understanding the performance of MIOLs, as such, various alterations could be made to improve the accuracy of defocus testing and analysis.

7.8.1.1 Curve fitting validation

In Chapter 2, a validation exercise was performed with two of the five IOLs included to assess the potential of the fitted curve to predict VA at given defocus intervals and comparison of these against measured values. To improve the rigour of this study, the validation exercise could have been carried out for all IOLs and participants.

7.8.1.2 Step size

Utilising 0.25D step sizes in Chapter 3, 4 and 5 would have provided a more detailed defocus profile, however this does significantly increase testing time for the subject and may be detrimental to results due to subject fatigue. In Chapter 3, had 0.25D steps been used, this may have improved the resolution of the defocus curve and altered effective addition power derived and possibly improved the accuracy of comparisons with the biometry formulae which are not constrained by dioptric intervals.

7.8.2 Mesopic conditions

No measurement of visual performance in mesopic conditions was undertaken for any of the MIOLs included in this thesis. The optical designs of these lenses indicate that performance

may be constrained by lighting levels, and as such, would be a useful clinical measure in comparisons between MIOLs and against monofocal control groups.

7.8.3 Assessment of Intermediate and Near visual acuity

In both Chapter 4 and 5, intermediate vision was assessed at 70cm and near vision assessed at 40cm. The patient preferred reading distance should also have been measured ideally. This would highlight the best achievable intermediate and near VA and the working distance required to achieve this. Arbitrary working distances can be optimised to suit the labelled addition power of the MIOLs to be studied, yet the results of Chapter 3 highlight that effective addition power can vary in individuals and as such this still may not allow maximum near VA to be assessed. However, the use of defocus curves mitigated for this limitation.

7.8.4 Validation of Questionnaire

A quality of vision questionnaire was used in both Chapter 4 and 5. Despite its use in a previous study, this questionnaire has not been validated, thus limiting the significance of its findings. This was mitigated somewhat by the use of a second validated questionnaire and where there was overlap, correlation was found to be good. Further validated questionnaires are available, but it was felt that they did not fully cover the patient reported outcomes as a whole, hence further work to create a comprehensive validated questionnaire for MIOL studies would be useful.

7.8.5 Dysphotopsia Analysis

A simulator was used to assess dysphotopsia in both Chapter 4 and 5. There were also questions pertaining to the effects of halos and glare in the questionnaire used. However, both of these methods introduce the notion of dysphotopsia and may bias patient reporting. Yet, opposite bias would occur if the concept of dysphotopsia was not introduced. In addition, there was no objective measure of photic phenomenon included in either study, thus future studies could consider the use of a halometer.

7.8.6 Spectacle Dependence Reporting

Chapter 4 was a randomised control trial, where patients present to clinic requiring cataract surgery. None of these patients indicated a desire for spectacle independence thus may be biased toward spectacle dependence. Whereas the subjects enlisted in Chapter 5 cohort studies presented with a motivation for spectacle independence, this is also likely to introduce bias. However, it is likely that most MIOL studies will continue to be cohort studies as the majority of patients have a certain expectation, including spectacle independence and thus are less likely to participate in a randomised control trial.

7.8.7 Toric Calculations

7.8.7.1 Corneal Power Measurements

The eye is marked pre-operatively at the slit lamp to improve accuracy of alignment of toric IOLs with respect to eye torsion when the patient is supine. However, no consideration of torsion is made when measuring corneal power, thus inaccuracies in corneal power measurements may contribute to expected final visual outcomes when implanting toric IOLs

7.8.7.2 Toric Calculation

Individual manufacturers toric calculators were used, and the mathematical detail of these calculators is not known, so the extent to which factors such as posterior corneal astigmatism is accounted for cannot be assessed. However other nomograms and calculators (Baylor Nomogram and Barrett calculator (Abulafia et al., 2016, Koch et al., 2013) exist that could have increased accuracy of pre-operative calculations, and provided a comparison to the manufactures calculators.

7.8.8 Accuracy of rotational analysis

The rotation of TIOLs was assessed but may have been adversely affected by the following;

7.8.8.1 Pre-operative marking

Marking the eye pre-operatively was done using a surgical marker with the subject sitting at a slit lamp. Once the subject was supine, the axis of implantation was confirmed with a Mendez gauge. However, this method is subject to various inaccuracies, by nature a surgical sterile marker provides a thick line marking, in addition, although cyclorotation is accounted for by this method, there is no accounting for head position whilst at the slit lamp (Buckhurst et al., 2010, Viestenz et al., 2006, Wolffsohn and Buckhurst, 2010). Digital surgical systems are now available which may reduce such inaccuracies (Kaur et al., 2017, Varsits et al., 2019, Webers et al., 2017).

7.8.8.2 Post-operative rotation

Although images were taken within 1 hour of surgery, the quality of these images was often compromised. Detrimental factors including post-operative corneal oedema, dilution of the pre-operative markings, thus difficulty to confirm implantation axis, and extensive pupil dilation, thus loss of iris features all contributed. All of these made imaging difficult and thus it was difficult to draw conclusions on the accuracy of alignment immediately post-operatively. The use of a surgical alignment system can provide digital images or video during surgery and immediately. Pre-operative images are also taken while the patient is upright to provide alignment, transferred electronically to the surgical system, thus negating the need for a surgical marker to be used.

7.8.8.3 Image Analysis

All images were assessed by only one masked observer. Such analysis is susceptible to human error, thus analysis by a second independent observer may have enhanced the accuracy of the analysis. It would also have been possible to assess inter-observer reliability.

In addition, the quality of the images taken has an impact on analysis. This was mitigated for in this study, by ensuring the same clinician took all images using the same slit lamp camera and lighting conditions.

7.8.9 Sample Size

Unequal sample sizes feature in Chapter 5, which may have compromised validity of comparison between the two groups. This was difficult to control due to the patient's choice

of MIOL. Overwhelmingly the characteristics of the trifocal were better suited to individuals' expectations.

In addition, although sample sizes were sufficient for our primary outcomes measures. The sample sizes were insufficient in both Chapter 5 and 6 to allow further division and thus subgroup analysis with respect to axial length and anterior chamber depth (Chapter 5) or with the rule, against the rule and oblique astigmatism (Chapter 6).

7.9 Future Work

This thesis highlighted areas for future investigation

7.9.1 Toric Multifocals

This thesis explored the use of TIOLs in astigmatic subjects and MIOLs in those with minimal astigmatism, however many individuals seek both astigmatic and presbyopic correction. Toric multifocals are readily available now from various manufactures and standardised comparative analysis is required.

7.9.2 Addition Power

Analysis of Trifocal and extended depth of focus IOLs is required in relation to prediction of spectacle plane addition power to confirm the validity of the Barrett II Universal formula for all MIOL styles. Also, larger studies sufficient variation in axial length, corneal curvature and anterior chamber depth will allow investigation of the effect of these parameters on addition power.

7.9.3 Questionnaire

The development and validation of a questionnaire suitable for MIOL studies to ensure patient reported outcomes including intermediate vision, near vision and dysphotopic symptoms are fully evaluated.

7.10 Conclusion

The use of premium IOLs in cataract surgery can lead to excellent visual acuity, high levels of spectacle independence and patient satisfaction, but these outcomes are not necessarily inevitable. A sound appreciation of the individual characteristics of differing IOLs must be held by clinicians in order to fully counsel their patient pre-operatively and thus select the most suitable IOL for an individual's needs. This thesis aimed to propose a standardise methodology for the assessment of MIOLs, and enhance existing methods (defocus analysis and prediction of addition power) to provide detailed clinical information. The necessary outcomes measures for assessment of MIOLs have been suggested which are readily reproducible in most clinical settings and easily repeatable. It focusses on both clinical measures and patient reported outcomes. It could be supplemented with the addition of an objective measure of photic phenomenon and testing of visual acuity, defocus and contrast sensitivity in mesopic conditions also. This protocol was able to highlight the differences between the various MIOL designs, thus uptake of such a protocol by the research community would encourage equitable comparison of current and future MIOL designs.

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Appendix One: Ethical Approval

A 1.1 Multifocal Cohort (Chapter 2 and Chapter 5)

A 1.2 Multifocal RCT (Chapter 3 and 4)

A 1.3 Extended Depth of Focus Cohort (Chapter 2 and Chapter 5)

A 1.4 Toric RCT (Chapter 6)

A 1.1 Multifocal Cohort

RESEARCH WITH PLYMOUTH UNIVERSITY

19th May 2014

CONFIDENTIAL

Dr Phillip Buckhurst
Room SF30
School of Health Professions
Peninsula Allied Health Centre
Plymouth University,
Derriford Road,
Plymouth
PL6 8BH

Dear Phillip

Application for Approval by Faculty Research Ethics Committee

Reference Number: 13/14-239
Application Title: **Assessment of visual function with multifocal intraocular lenses**

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for three years, after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact Sarah Jones (email sarah.c.jones@plymouth.ac.uk).

Yours sincerely

Professor Michael Sheppard, PhD, AcSS,
Chair, Research Ethics Committee -
Faculty of Health & Human Sciences and
Peninsula Schools of Medicine & Dentistry

Faculty of Health & Human Sciences
Plymouth University
Drake Circus
Plymouth PL4 8AA

T +44 (0)1752 585339
F +44 (0)1752 585328
E sarah.c.jones@plymouth.ac.uk
W www.plymouth.ac.uk

Professor Michael Sheppard
CQSW BSc MA PhD AcSS
Chair, Faculty Research Ethics Committee

A 1.2 Randomised Clinical Trial BiFlex M multifocal IOL

NHS
Health Research Authority
NRES Committee South West - Cornwall & Plymouth
Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421390
Fax:01173420445

09 March 2015

Mr Rajesh Aggarwal
BMI Southend Hospital
Fairfax Avenue
Westcliff-on-sea
SS0 9AG

Dear Mr Aggarwal

Study title:	**Randomised clinical trial of the Biflex M multifocal intraocular lens**
REC reference:	**15/SW/0027**
IRAS project ID:	**165928**

Thank you for your letter of 6th March 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

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

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

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

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

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

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

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

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

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

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

Ethical review of research sites

NHS sites

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

"Conditions of the favourable opinion" below).

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Covering Letter for ethics application]	V1	23 January 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsors insurance]	V1	23 January 2015
GP/consultant information sheets or letters [Letter to GP]	V1	23 January 2015
IRAS Checklist XML [Checklist_23012015]		23 January 2015
IRAS Checklist XML [Checklist_06032015]		06 March 2015
Other [Validated questionnaire 2]	V1	23 January 2015
Other [CV of second supervisor]	V1	23 January 2015
Participant consent form [Consent form]	V1	23 January 2015
Participant information sheet (PIS) [Participant information sheet]	V2	06 March 2015
REC Application Form [REC_Form_23012015]		23 January 2015
Research protocol or project proposal [Protocol V1]	V1	23 January 2015
Summary CV for Chief Investigator (CI) [CV of Chief Investigator]	V1	23 January 2015
Summary CV for student [CV of PhD student]	V1	23 January 2015
Summary CV for supervisor (student research) [Cv of Main supervisor]	V1	23 January 2015
Validated questionnaire [NAVQ validated questionnaire]	V1	23 January 2015

Statement of compliance

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

After ethical review

Reporting requirements

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

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol

- Progress and safety reports
- Notifying the end of the study

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

User Feedback

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

HRA Training

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

15/SW/0027	**Please quote this number on all correspondence**

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

Yours sincerely

Canon Ian Ainsworth-Smith
Chair

Email: nrescommittee.southwest-cornwall-plymouth@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Graham Sewell, Head of School of Health Professions, University of Plymouth*
Mr Rajesh Aggarwal, BMI Southend Hospital

A 1.3 Extended Depth of Focus Cohort

RESEARCH WITH PLYMOUTH UNIVERSITY

1st September 2014

CONFIDENTIAL

Dr Phillip Buckhurst
Room SF30
School of Health Professions
Peninsula Allied Health Centre, Plymouth University
Derriford Road
Plymouth
PL6 8BH

Dear Phillip

Application for Approval by Faculty Research Ethics Committee

Reference Number: 13/14-271
Application Title: Visual Performance of patients bilaterally implanted with the TECNIS® Symfony Extended Range of Vision IOL

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for three years, after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact Sarah Jones (email sarah.c.jones@plymouth.ac.uk).

Yours sincerely

Professor Michael Sheppard, PhD, FAcSS
Chair, Research Ethics Committee -
Faculty of Health & Human Sciences and
Peninsula Schools of Medicine & Dentistry

Faculty of Health & Human Sciences
Plymouth University
Drake Circus
Plymouth PL4 8AA

T +44 (0)1752 585339
F +44 (0)1752 585328
E sarah.c.jones@plymouth.ac.uk
W www.plymouth.ac.uk

Professor Michael Sheppard
CQSW BSc MA PhD AcSS
Chair, Faculty Research Ethics Committee

A 1.4 Randomised Clinic Trial Toric IOL

RESEARCH WITH PLYMOUTH UNIVERSITY

15TH September 2014

CONFIDENTIAL

Dr Phillip Buckhurst
Room SF30
School of Health Professions
Peninsula Allied Health Centre
Plymouth University
Derriford Road
Plymouth
PL6 8BH

Dear Phillip

Application for Approval by Faculty Research Ethics Committee

Reference Number: 13/14-278
***Application Title:* A randomised intra-patient comparison of closed loop and plate haptic toric, aspheric, aberration neutral, hydrophilic acrylic intraocular lenses in patients with bilateral astigmatism**

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for three years, after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact Sarah Jones (email sarah.c.jones@plymouth.ac.uk).

Yours sincerely

Professor Michael Sheppard, PhD, FAcSS
Chair, Research Ethics Committee -
Faculty of Health & Human Sciences and
Peninsula Schools of Medicine & Dentistry

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Plymouth PL4 8AA

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W www.plymouth.ac.uk

Professor Michael Sheppard
CQSW BSc MA PhD AcSS
Chair, Faculty Research Ethics Committee

Health Research Authority
NRES Committee South West - Exeter
Whitefriars
Level 3
Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421390
Fax:01173420445

27 March 2015

Mr Rajesh Aggarwal
BMI Southend Hospital
Fairfax Avenue
Westcliff-on-sea
East Sussex
SS0 9AG

Dear Mr Aggarwal

Study title:	**A Randomised Intra-patient Comparision of Closed Loop and Plate Haptic Toric, Aspheric Aberration Neutral Hydrophilic Acrylic Intraocular Lenses in Patients with Bilateral Astigmatism**
REC reference:	**15/SW/0025**
Protocol number:	**N/A**
IRAS project ID:	**168791**

Thank you for your letter of 26th March 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

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

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

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

1. Amend the consent form to refer to the new version number and date from the latest PIS.

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

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

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

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

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

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

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

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

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

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

Ethical review of research sites

NHS sites

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

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Covering Letter for ethics application]	V1	02 December 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsors insurance]	V1	02 December 2014
GP/consultant information sheets or letters [Letter to GP]	V1	02 December 2014
IRAS Checklist XML [Checklist_26032015]		26 March 2015
Other [CV of second supervisor]	V1	15 January 2015
Other [Cover letter and response to additional reviewers questions]	V2	11 March 2015
Participant consent form [consent form V2]	V2	11 March 2015
Participant information sheet (PIS) [Participant information sheet V3]	V3	26 March 2015
REC Application Form [REC_Form_13012015]		13 January 2015
Research protocol or project proposal [Protocol V1]	V1	02 December 2014
Summary CV for Chief Investigator (CI) [CV of Chief Investigator]	V1	02 December 2014
Summary CV for student [CV of PhD student]	V1	02 December 2014
Summary CV for supervisor (student research) [CV for the two supervisors Hetal and Phillip Buckhurst]	V2	15 January 2015

Statement of compliance

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Ethics Committees in the UK.

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15/SW/0025	**Please quote this number on all correspondence**

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

Yours sincerely

pp. G Sheehan

Dr Denise Sheehan
Chair

Email: nrescommittee.southwest-exeter@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

Appendix Two: Questionnaire

Quality of Vision Questionnaire

If you have any questions regarding the completion of this questionaire, please ask during your consultation.
The questions deal primarily with vision at three distinct distances, referred to as Distance (e.g. TV, driving, theatre), Intermediate (e.g. Computer, reading music) and Near (e.g reading a book, sewing)
Please tick

Q1. Do you see well without glasses at the following distances?

Distance	☐ yes	☐ no
Intermediate	☐ yes	☐ no
Near	☐ yes	☐ no

Q2. How often do you wear glasses or contact lenses?

☐ always ☐ never ☐ occasionally

Q3. If you wear glasses/contact lenses, please specify what type? (please state all)

☐ distance ☐ near ☐ intermediate ☐ bifocals ☐ varifocals

Q4. Are you satisfied with your vision since your surgery?

☐ yes ☐ no

Please rate the level of your satisfaction.

☐ entirely ☐ mostly ☐ moderately ☐ poorly ☐ not at all

Q5. Please estimate on a scaling from 1 to 7 how well you can do the following activities without glasses:
Please leave blank any that are not applicable to you.
1 = without any problem and 7 = very difficult: (If you are not able to do one activity due to reasons other than your vision please do not mark a box)

	Not difficult			Medium difficulty		Very difficult	
	1	2	3	4	5	6	7
Reading a newspaper	☐	☐	☐	☐	☐	☐	☐
Reading a book	☐	☐	☐	☐	☐	☐	☐
Reading labels on medication	☐	☐	☐	☐	☐	☐	☐
Cooking/ Eating	☐	☐	☐	☐	☐	☐	☐
Shopping	☐	☐	☐	☐	☐	☐	☐
Using a computer	☐	☐	☐	☐	☐	☐	☐
Walking/Mobility	☐	☐	☐	☐	☐	☐	☐
Driving	☐	☐	☐	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐	☐	☐	☐
Reading street signs	☐	☐	☐	☐	☐	☐	☐
Recognising faces	☐	☐	☐	☐	☐	☐	☐

Q6. Please assess on a scale from 1 to 7 how severe you experience the following visual problems.

1 = no problem and 7 = very difficult (with glasses if needed):

	Not difficult			Medium difficulty		Very difficult	
	1	2	3	4	5	6	7
Night vision	☐	☐	☐	☐	☐	☐	☐
Glare at night	☐	☐	☐	☐	☐	☐	☐
Halos	☐	☐	☐	☐	☐	☐	☐
Starbursts	☐	☐	☐	☐	☐	☐	☐
Ghost images	☐	☐	☐	☐	☐	☐	☐
Glare in daylight	☐	☐	☐	☐	☐	☐	☐
Depth perception	☐	☐	☐	☐	☐	☐	☐
Double vision	☐	☐	☐	☐	☐	☐	☐
Fluctuating vision	☐	☐	☐	☐	☐	☐	☐
Other (please specify)	☐	☐	☐	☐	☐	☐	☐

Q7. How often do you go out in the evenings?

☐ never ☐ occasionally ☐ regularly

Q8. How often do you drive a car at night?

☐ rarely ☐ occasionally ☐ regularly

☐ I never drive at night ☐ I don’t drive at all