The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes

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Despite the known visual and pathological implications of hyperopia, there has been inertia to address the modulation of refractive error in these individuals.

Imposing relative peripheral hyperopic defocus using centre-near multifocal contact lenses accelerates axial growth in isohyperopic children.
Axial growth and refractive error did not change during the 6 months prior to intervention in the intervention or control group. Axial growth across the 2-year period of intervention was 0.17 mm in the intervention group *versus* 0.06 mm in the control group. Refractive error change across the same period was -0.26 D in the intervention group and +0.01 D in the control group. Axial growth and refractive error during the final 6 months without intervention did not change in either group. The overall difference in axial growth between groups was significant whereas the change in refractive error was not.

Imposing relative peripheral hyperopic defocus using centre-near multifocal contact lenses does not accelerate axial growth nor reduce refractive error in anisohyperopic children.
In this paired eye study, axial growth and refractive error did not change during the 6 months prior to intervention in either eye. Axial growth across the 2-year period of intervention was 0.11 mm in the intervention eye *versus* 0.15 mm in the control eye. Refractive error change across the same period was -0.23 D in the intervention eye and -0.27 D in the fellow eye. Axial growth and refractive error during the final 6 months without intervention did not change in either group. The overall change in axial growth was greater in the control eye than the intervention eye, whereas the reduction in refractive error was comparable.

Axial length measures are comparable and repeatable under pre- and post-cycloplegic conditions.

Refractive error measures are comparable and repeatable at discrete time intervals after the instillation of a cycloplegic agent.

Keywords: hyperopia, refractive error, peripheral defocus, contact lenses

For Clarence

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List of Abbreviations

ACD	Anterior chamber depth
AL	Axial length
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
BF	Bifocal
BFSCL	Bifocal soft contact lens
CC	Corneal curvature
CI	Confidence interval
CL	Contact lenses
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error
CS	Contrast sensitivity
CSF	Contrast sensitivity function
D	Dioptres
DF	Dual focus
DIMS	Defocus incorporated multiple segments
DISC	Defocus incorporated soft contact lens
Dk/t	Oxygen transmissibility
DVA	Distance visual acuity
DV	Distance vision
FNS	Frisby Near Stereotest
GAT	Goldmann applanation tonometry
HCl	Hydrochloride
HOA	High order aberration
ILM	Internal limiting membrane
IOP	Intraocular pressure
LCA	Longitudinal chromatic aberration

LoA	Limits of agreement
LogMAR	Logarithm of the minimum angle of resolution
LOA	Low order aberration
MF	Multifocal
MRI	Magnetic resonance imaging
MSE	Mean spherical equivalent
NICER	Northern Ireland Childhood Errors of Refraction
NVA	Near visual acuity
OK	Orthokeratology
PAL	Progressive addition lens
PBF	Prismatic bifocal
PCI	Partial coherence interferometry
RAF	Royal Air Force
RGP	Rigid gas permeable
RPE	Retinal pigment epithelium
RPH	Relative peripheral hyperopia
RPHD	Relative peripheral hyperopic defocus
RPMD	Relative peripheral myopic defocus
+SA	Positive spherical aberration
SEM	Standard error of the mean
SF	Spatial frequency
SRRG	Soft radial refractive gradient
SV	Single vision
TNO	TNO Randot Stereotest
VA	Visual acuity
VCD	Vitreous chamber depth
WT	Wearing time

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1.0 Literature review

1.1 Introduction

Hyperopia is a known risk factor for the development of strabismus and amblyopia (Colburn *et al*., 2010). In addition to visual consequences, there is a growing body of evidence that uncorrected hyperopia (Williams *et al*., 2005) and anisohyperopia (Narayanasamy *et al*., 2014) may have a negative impact upon educational attainment and visuocognitive and visuomotor skills (Atkinson *et al*., 2007). Hyperopia occurs as a consequence of insufficient ocular growth and a failure to emmetropise in childhood with the majority of hyperopic refractive errors resulting from an eye that is too short for its refractive power (Strang *et al*., 1998).

Currently hyperopia receives far less attention from research than myopia, even though the impact of moderate to high levels of hyperopia, especially in one eye, can lead to amblyopia if not corrected fully at a young age (Kulp *et al*., 2014). Although myopia has public health implications in an adult population (Flitcroft, 2012; Ohno-Matsui *et al*., 2021), within a paediatric population, hyperopia and anisometropia create the greatest ocular morbidity (Flitcroft, 2014).

To understand the potential to modulate refractive error in hyperopes, it is important to explore the general literature. As such, this chapter will review human emmetropisation and how its failure leads to hyperopia. The optical approaches taken to control myopia progression will also be considered to hypothesise how these principles could be applied in the context of hyperopia.

1.2 Human emmetropisation

1.2.1 Background

Emmetropisation describes a developmental process that matches optical power to axial length (AL) such that the unaccommodated eye is focused at distance (Troilo *et al*., 2019).

Human refraction differs from many other biological variables, such as height, which typically follow a normal distribution (Limpert *et al*., 2001). In fact, beyond 3 months of age, human refraction has a leptokurtic distribution, that is to say, a high peak and a distribution clustered around the mean, which is also negatively skewed (Flitcroft, 2014). Intriguingly, the ocular parameters that contribute to final refraction, namely corneal curvature (CC), anterior chamber depth (ACD), lens thickness and AL are distributed in a more typically Gaussian distribution (Flitcroft, 2014). The high prevalence of emmetropic and low hyperopic refractive errors in the human population has led to the hypothesis that there must be a mechanism in place to minimise refractive errors by regulation of eye growth; this is supported by the literature which shows that such a mechanism exists in human infants (Ehrlich *et al*., 1997; Mutti *et al*., 2005). Indeed, the mechanism responsible for aligning the optical and structural development of the eye to permit successful emmetropisation appears to be visually driven (Mutti *et al*., 2009).

1.2.2 Phases of emmetropisation

Half a century ago, the work of Sorsby and colleagues established that around 50% of postnatal eye growth in normal eyes occurs within the first 12 to 16 months of life, followed by a decade of decelerated axial elongation before stopping no later than the age of 13 years (Sorsby *et al*., 1961; Sorsby and Leary, 1970). On the basis of these observations, it is considered that emmetropisation can be broadly split into two distinct phases: a rapid infantile phase and a slow juvenile phase.

The initial, rapid infantile phase of emmetropisation, is defined as the period from birth up to 3 years of age (Sorsby and Leary (1970) where the components of the eye need to make significant adjustments to keep pace with axial elongation. During the first 12 months of life, the power of the eye drops markedly from 90 Dioptres (D) at birth to 75 D (Wood *et al*., 1996). The Gaussian distribution of refractive error observed at 3 months becomes leptokurtic by 9 months of age (Mutti *et al*., 2005).

Neonates present with a wide refractive range, which decreases within the first year of life due to changes to CC (Inagaki, 1986; Mutti *et al*., 2005), AL (Fledelius and Christensen, 1996; Mutti *et al*., 2005; Fledelius *et al*., 2014), and crystalline lens power (Gordon and Donzis, 1985; Mutti *et al*., 2005). The reduction in hyperopia that occurs between the ages of 3 months and around 3 years of age is greater than which can be attributed to a passive process of emmetropisation, that is to say, through normal eye growth; therefore, an active feedback process to modulate axial growth must also play a part (Flitcroft, 2014).

The slower juvenile phase of emmetropisation is considered to take place from the age of 3 years up to the beginning of the teenage years. Between 3 and 6 years of age, emmetropisation continues but at a slower pace and the distribution remains leptokurtic but positively skewed at this stage of life (Flitcroft, 2014). After the age of 6 years, refraction starts to display divergence based upon geographical location. For instance, in Australia the distribution becomes more leptokurtic due to low levels of myopia and hyperopia (French *et al*., 2012) whereas in most populations, especially in the East, leptokurtosis reduces and the distribution becomes negatively skewed due to a higher prevalence of myopia (French *et al*., 2012; Watanabe *et al*., 1999). In the Far East, and other parts of the world, including the UK (Logan *et al*., 2011; McCullough *et al*., 2016), myopia may present as early as 6 years of age (Matsumara and Hirai, 1999; Lin *et al*., 2004).

1.2.3 Ocular structure changes during emmetropisation

1.2.3.1 Cornea

There is a rapid change in corneal power during the first 2 to 4 weeks of life with a reduction of 3 D reported, followed by a slowing of this trend after 8 weeks as measured using an adapted automated keratometer (Inagaki, 1986). Nevertheless, keratophakometry shows that the power of the cornea continues to reduce between the ages of 3 and 9 months, by approximately 1 D (Mutti *et al*., 2005). Despite this rapid pace of change in early life, which

sees average corneal power reduce from 47 to 48 D at infancy to 43 to 44 D by 9 months of age, it remains largely stable throughout childhood with little reduction in power seen thereafter (Zadnik *et al*., 2003; Mutti *et al*., 2005; Jones *et al*., 2005).

1.2.3.2 ACD

Assessment using A-scan ultrasonography has shown that ACD increases by 0.26 mm between 3 and 9 months of age (Mutti *et al*., 2005). The rapid growth phase sees ACD increasing by 0.9 to 1 mm from birth to 18 months of age, followed by modest growth of 0.3 to 0.4 mm by age 7 years (Larsen, 1971a). From here, there is a slow phase, with growth of less than 0.1 mm between 8 and 13 years of age (Larsen, 1971a; Zadnik *et al*., 2003).

1.2.3.3 Lens

Normal development of the crystalline lens throughout childhood, as measured using A-sacn ultrasonography, is characterised by thinning, flattening and a decrease in power in order to achieve emmetropia by maintaining a balance with increasing AL (Mutti *et al*., 2012). A thinning of the crystalline lens occurs between 3 and 9 months of age with a flattening of both the anterior and posterior radii along with a small increase in equivalent refractive index leading to a net decrease in lens power of just over 3.5 D (Mutti *et al*., 2005). This decrease in crystalline lens power is around 3 times greater than the reduction in corneal power over this period. The mean thickness of the crystalline lens appears to decrease by approximately 0.3 mm during the first year of life and then by around 0.2 mm by the age of 8 to 10 years, whereupon this flattening process appears to stop or slow almost to the point of stopping (Larsen, 1971b).

Between the ages of 6 and 14 years, ultrasound (Larsen, 1971b;) and videophakometry (Zadnik *et al*., 2003) show that thinning and flattening of the crystalline lens continues. Overall, the flattening of radii of curvature of the crystalline lens contributes towards an overall loss in equivalent power of about 18 to 19 D by 14 years of age. The curvature changes are accompanied by a decrease in equivalent refractive index from 1.45 in early infancy to about

1.42 by 10 years of age; this decrease in refractive index is responsible for almost half of the reduction in equivalent crystalline lens power (Mutti *et al*., 2005; Jones *et al*., 2005).

1.2.3.4 AL

A-scan ultrasonography demonstrates a rapid growth phase to AL in early life (Mutti *et al*., 2005) with an increase of 3.7 to 3.8 mm from birth to 18 months, followed by 1.1 to 1.2 mm of elongation by 5 years of age and finally a further 1.3 to 1.4 mm by the age of 13 years (Larsen, 1971c). An increase in vitreous chamber depth (VCD) is primarily responsible for this axial elongation. From birth to 18 months of age, VCD increases by 3 mm followed by slower growth of 1.3 mm up to the age of 7 years and then a further 1.1 mm during the early teenage years and beyond (Larsen, 1971d).

1.2.3.5 Summary

Despite the reduction in corneal and crystalline lens power during infancy, these adjustments do not correlate with the change in refractive error. However, AL changes are correlated with refractive error reduction with increases in axial elongation aligned to a decrease in hyperopia. In other words, the modulation of axial growth with respect to the initial level of refractive error appears to be more influential in the emmetropisation process than changes to other ocular components, namely the cornea and crystalline lens. Hence, the guidance of ocular growth towards reaching emmetropia appears to be an active rather than a passive mechanism (Mutti *et al*., 2005).

1.2.4 Failures of emmetropisation

1.2.4.1 Background

The majority of emmetropisation occurs early on in life and is mostly complete by 6 years of age (Flitcroft, 2014). If a significant degree of refractive error persists beyond this age, then this is due to: an initial refractive error that is too high to be corrected by the emmetropisation

process; a failure of the emmetropisation process itself; or a combination of the two. So, refractive errors present at the age of 6 years are considered to be primary failures in the process of emmetropisation (Flitcroft, 2013). The standard deviation of refractive error is lowest at this age as is the proportion of those with significant ametropia. With this in mind, it seems that the aetiology of refractive errors is not dominated by a primary failure in emmetropisation (Flitcroft, 2014).

At 6 years of age, the distribution of refractive error is positively skewed demonstrating the different courses of myopia and hyperopia. In other words, hyperopia is predominantly due to a primary failure of emmetropisation whereas the onset of myopia typically occurs beyond the age of 6 years in those who have successfully achieved emmetropia earlier on in childhood and is considered to be a secondary failure of emmetropisation (Flitcroft, 2014).

1.2.4.2 Hyperopia

The eye appears to be able to direct its growth in response to the underlying level of ametropia, guided by feedback from visual input (Saunders *et al*., 1995; Mutti *et al*., 2005). The extent of exposure to hyperopic defocus could provide the visual cue required to allow the eye to detect the magnitude of refractive error and increase AL accordingly to reduce its level of hyperopia in early childhood (Mutti *et al*., 2009). Naturally, this exposure to hyperopic defocus in hyperopic infants is a function of both the magnitude of refractive error and the accommodative response.

The accommodative response in early infancy is variable (Candy and Bharadwaj, 2007) although dynamic capability seems to be present at 2 months of age (Tondel and Candy, 2007). Despite initial immaturities in the accommodative response, infants appear capable of maintaining accurate *average* levels of accommodation across a moderate range of hyperopic refractive errors as early as 3 months of age (Mutti *et al*., 2009) reaching adults levels as soon as 5 months of age (Brookman, 1983; Sokol *et al*., 1983). The variability in infant

accommodation and resultant hyperopic defocus signals may form the basis for emmetropisation. It follows, that if an infant is exposed to a higher level of hyperopic defocus then it may be expected that a greater refractive change would occur during emmetropisation (Mutti *et al*., 2009). However, the evidence shows that infants with high levels of hyperopia are less likely to achieve an emmetropisation outcome by 18 months of age (Mutti *et al*., 2009). The findings by Mutti *et al*., 2009 show that deficiencies in emmetropisation at higher levels of hyperopia are related to poorer accommodation and higher levels of defocus; this is contrary to the expectation that emmetropisation would be more likely in the presence of greater levels of hyperopic defocus exposure. Although the pace of growth is related to the initial level of refractive error (Mutti *et al*., 2005), the likelihood of emmetropisation reduces if the magnitude exceeds its operating range (see Figure 1.1). Others have found that during infancy, emmetropisation occurs more rapidly in those with 'high' refractive errors, although these measures were obtained without cycloplegia and limited to an upper range of +4.25 D (Saunders *et al*., 1995).

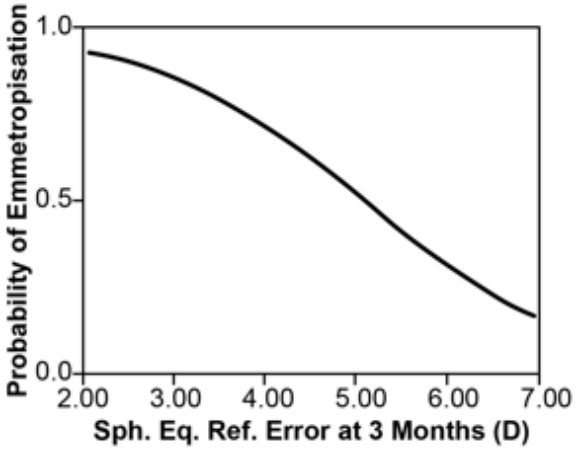

Figure 1.1 The probability of reaching +2.00 D by 18 months of age as a function of cycloplegic refractive error at 3 months of age. Adapted from Mutti *et al*., 2009

Evidence that similar amounts of defocus exists across moderate levels of hyperopia does not point to a simple model of emmetropisation that is guided by hyperopic defocus (Mutti *et al*., 2009). It has been postulated that other emmetropisation models driven by defocus may be at play. For instance, the possibility that a consistent level of defocus above a particular threshold

may trigger a rapid growth phase that reduces hyperopia (Mutti *et al*., 2009). This fast phase of growth may then switch to a slower growth phase once emmetropia is achieved and defocus falls below the threshold level. In this model, the duration of rapid growth would be dictated by the magnitude of the initial refractive error and limited by a 'stop' signal such as the presence of minimal distance defocus (Norton *et al*., 2006). Another possible model for emmetropisation is that the rate of axial growth is related to the level of accommodative effort. In this scenario, the level of hyperopia could be the driver for a dose-dependent signal for emmetropisation by providing the stimulus to accommodation rather than through defocus. This latter model is supported by the fact that similar levels of defocus are present across a modest range of refractive errors where emmetropisation occurs indicating that an accurate accommodative response is a factor in this success (Mutti *et al*., 2009). Further, the failure of emmetropisation at higher levels of hyperopia may be the result of a lack of effort to accommodate to compensate for the refractive error as seen in animal work (Smith and Hung, 1999).

The probability of emmetropisation during infancy also appears to be linked to the level of visual acuity (VA) (Mutti *et al*., 2009). Emmetropisation in hyperopic infants is more likely if VA is above a certain level whereas poorer or unmeasurable vision seems to impair this process (see Figure 1.2). Of course, acuity is also linked to the underlying level of refractive error.

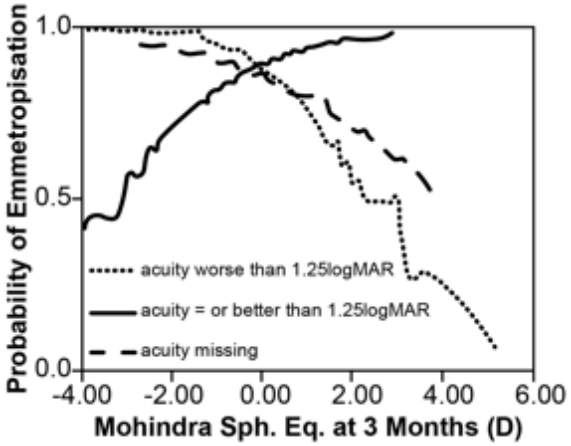

Figure 1.2 The probability of reaching +2.00 D by 18 months of age as a function of the level of visual acuity group and Mohindra retinoscopy results at 3 months of age. Adapted from Mutti *et al*., 2009

1.2.4.3 Myopia

While the process of emmetropisation does not appear to have altered in recent decades, the distribution of refractive error in adults has changed dramatically due to an increase in myopia prevalence and its geographical variation over time (Flitcroft, 2014). The typical onset of myopia beyond the age of 6 years arises after several years of relatively stable refraction (Thorn *et al*., 2004). The initial phase of myopia progression adopts a linear path (Goss and Winkler, 1983) before slowing, although continuing to increase, throughout childhood and well into adulthood (Dirani *et al*., 2008). It is clear that increasing AL is the primary driver of myopia progression (Chung *et al*., 2002; Gwiazda *et al*., 2003; Chua *et al*., 2006).

Despite extensive literature in the field, the triggers for the accelerated phase of myopia progression at onset and the mechanisms for the slowing of this process are still not fully understood (Flitcroft, 2014).

1.2.4.4 Anisometropia

Stochastic factors also appear to play a part in the aetiology of refractive errors as inferred by the existence of anisometropia. In anisometropes, despite sharing the same genome and environmental exposure, each eye emerges with a different refractive error. Anisometropia can be present early on in life with subsequent ocular development complicated by amblyopia (Flitcroft, 2014; Flitcroft *et al*., 2020). However, anisometropia often develops later, in both hyperopes and myopes (Abrahamsson *et al*., 1990, Deng and Gwiazda, 2012). Anisometropia is also linked to the magnitude of the refractive error, that is to say, higher levels of myopia, hyperopia, and astigmatism, are associated with an increasing frequency of anisometropia (Qin *et al*., 2005; Deng and Gwiazda, 2012). So, it seems that the regulated pattern of growth at around the age of 6 years exhibits increasing variability between individuals and between the two eyes of a single subject (Flitcroft, 2014).

The relationship between amblyopia and emmetropisation is still not clearly understood (Flitcroft, 2014). It has been shown in monkeys that induced amblyopia leads to hyperopia in the amblyopic eye (Kiorpes and Wallman, 1995) and that the development of amblyopia leads to a failure in compensatory growth to imposed defocus (Smith *et al*., 1999). The situation is less clear cut in humans, although some studies suggest that anisometropia may be a consequence of amblyopia as much as a cause (Lepard, 1975; Nastri *et al*., 1984). It has also been demonstrated that patterns of vitreous chamber growth are different between an amblyopic eye and its fellow eye (Burtolo *et al*., 2002).

1.2.4.5 Summary

The model of human emmetropisation in early life is in keeping with an optically guided model as predicted by animal work (Flitcroft, 2014). Rates of emmetropisation appear to be correlated with the magnitude of the initial refractive error, at least up to a moderate range (Saunders *et al*., 1995). Hyperopes with higher levels of refractive error appear to fall victim to a primary failure of emmetropisation, while later in childhood, secondary failures of emmetropisation are characterised by a rapid refractive acceleration in the direction of myopia.

1.3 Childhood refractive error

1.3.1 Prevalence

The distribution of refractive error has changed in recent decades and continues to do so as a result of an alarming increase in the worldwide prevalence of myopia, which is already at epidemic levels in some countries (Holden *et al*., 2016; Sankaridurg *et al*., 2021). By 2050, it is estimated that around half of the population will be myopic with ~ 10% having levels of 5.00 D or more (Holden *et al*., 2016). Despite the broad myopic shift in refractive error, there still represents a significant burden that results from other types of ametropia, namely hyperopia (Kleinstein *et al*., 2003; Logan *et al*., 2011; McCullough *et al*., 2016) and anisometropia (Deng and Gwiazda, 2012; O'Donoghue *et al*., 2013).

1.3.1.1 Hyperopia and myopia

Given the geographical variance in the prevalence of myopia, location-specific differences in hyperopia also exist (Hashemi *et al*., 2018). While different cut off points are used in the literature to define hyperopia, the typical criterion is a post-cycloplegic mean spherical equivalent (MSE) refractive error of ≥ +2.00 D and ≥ +0.50 D for non-cycloplegic refraction (Hashemi *et al*., 2018). A meta-analysis of 45 studies identified an overall estimate of post-cycloplegic childhood hyperopia prevalence of 4.6%, where under 20 years of age was used to define 'children'. A breakdown of hyperopia prevalence by WHO region cited in the review is summarised in Table 1.1 (Hashemi *et al*., 2018).

WHO region	Estimated hyperopia prevalence (%) (95% CI)
Africa	3.0 (1.8-4.3)
Americas	14.3 (13.4-15.2)
Southeast Asia	2.2 (1.2-3.3)
Europe	9.0 (4.3-13.7)
Eastern Mediterranean	6.8 (4.9-8.6)
Western Pacific	3.1 (1.9-4.3)
All	**4.6 (3.9-5.2)**

Table 1.1 Estimates of hyperopia (post-cycloplegic MSE of ≥ +2.00 D) prevalence by World Health Organization (WHO) region (95% confidence intervals (CI)). Adapted from Hashemi *et al*., 2018

A UK study in 2005 showed that the prevalence of (non-cycloplegic) hyperopia in an undergraduate university cohort was similar between the two predominant ethnic groups at 18.8% and 17.3% for white and British Asian participants, respectively (Logan *et al*., 2005). In the same study, levels of myopia at that time were cited as 50% for white participants and 53.4% for British Asians. The literature shows from studies in children that the distribution of

refractive errors in the UK is changing (Logan *et al*., 2011; McCullough *et al*., 2016), while at the same time demonstrating ethnic differences (Logan *et al*., 2011).

The Aston Eye Study revealed that the overall prevalence of hyperopia (mean post-cycloplegic MSE ≥ +2.00 D in either/both eyes) in a mixed ethnic cohort was 12.3% for children aged 6 to 7 years *versus* 5.4% for those aged 12 to 13 years (Logan *et al*., 2011). In white European children, the hyperopia prevalence was 22.9% at 6 to 7 years compared to 10.3% in South Asian children. At 12 to 13 years, the rates of hyperopia decreased to 10.4% *versus* 2.6% in white European and South Asian children, respectively. In contrast, the prevalence of myopia (mean post-cycloplegic MSE ≤ -0.50 D in either/both eyes) was 9.4% for those aged 6 to 7 years compared to 29.4% for those aged 12 to 13 years. In the older group, the prevalence of myopia was 36.8% for South Asian children compared to 18.6% for white Europeans.

The Northern Ireland Childhood Errors of Refraction (NICER) study reports longitudinal refractive data for white UK children over a 6-year period for 2 cohorts aged 6 to 7 years and 12 to 13 years at baseline (McCullough *et al*., 2016). For the younger participants, the prevalence of hyperopia (mean post-cycloplegic MSE ≥ +2.00 D) at baseline was 21.7% (21.0% in males; 22.4% in females) and decreased to 14.2% (13.3% in males; 15.0% in females) after 6 years. In the older age group, the proportion of hyperopes at baseline was 15.0% (17.4% in males; 13.3% in females) and 17.7% (19.4% in males; 16.4% in females) at the 6-year timepoint. The average annual rate of change in MSE refractive error was -0.09 D and +0.02 D in the younger and older participants, respectively. The proportion of myopes (mean post-cycloplegic MSE ≤ -0.50 D) at baseline in the younger group was 1.9%, rising to 14.6% over the course of the 6-year study. In the older participants, myopia prevalence was 16.4% at baseline and 18.6% after 6 years. There were no significant differences between gender in the annual rate of MSE refractive change for myopes in either age group.

Intriguingly, comparison of data from the NICER study with children in Australia shows differences in rates of hyperopia and myopia at two timepoints in childhood (French *et al*., 2012). In 6- to 7-year-old children in Sydney, rates of hyperopia were lower in children in Sydney (12.0%) than children in Northern Ireland (22.3%). Similarly, the prevalence at age 12 to 13 years was also lower in the Australian cohort compared to Northern Ireland at 4.4% and 11.8%, respectively, although the MSE refractive error was higher at +0.83 D in Australian children compared to +0.66 D in the UK-based cohort.

Elsewhere in the world, findings from the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study (Kleinstein *et al*., 2003) in the US, mirrors the higher rates of myopia seen in UK-based Asian children compared to those from other ethnic backgrounds. Overall rates of myopia were 9.2%, but specifically, the data showed that in children aged 5 to 17 years, Asians had the highest prevalence of myopia (18.5%) followed by Hispanics (13.2%), while children of European ancestry had the lowest prevalence (4.4%), which was similar to African Americans (6.6%). Data for hyperopes (mean post-cycloplegic refraction in each principal meridian ≥ +1.25 D) from the same study showed an overall prevalence of 12.8% with highest rates seen in whites (19.3%), followed by Hispanics (12.7%), African Americans (6.4%) and Asians (6.3%).

1.3.1.2 Anisometropia

During the first year of life, the prevalence of anisometropia decreases (Wood *et al*., 1995; Mayer *et al*., 2001) but remains relatively stable throughout early (Abrahamsson *et al*., 1990; Borchert *et al*., 2010; de Vries, 1985) and late childhood (de Vries, 1985; Dobson *et al*., 2008), although higher rates are associated with childhood hyperopia (Deng and Gwiazda, 2012) and myopia (Tong *et al*., 2006; Deng and Gwiazda, 2012). The stable rates of anisometropia are maintained as a consequence of as many children losing as those developing this refractive status (Abrahamsson and Sjöstrand, 1996).

Although there does not appear to be a standard definition of anisometropia, an interocular MSE difference of ≥ 1.00 D appears to be a common criterion (Qin *et al*., 2005; Huynh *et al*., 2006; Dobson *et al*., 2008; O'Donoghue *et al*., 2013). Others highlight that in strict terms, any difference in interocular refractive error could be classified as anisometropia but as a result of test-retest variability in measurement, a difference of ≥ 0.75 D should be reserved for a clinically significant definition (Barrett *et al*., 2013).

Insight from the NICER study provides useful data on the prevalence of anisometropia at 2 key timepoints during childhood (O'Donoghue *et al*., 2013). At age 6 to 7 years, the proportion of anisometropes (post-cycloplegic MSE ≥ 1.00 D) among white children in the UK was 8.5% and similar to levels in the 12 to 13 age group at 9.4%. In the older children, the results also highlighted that anisometropia is more common in those with moderate hyperopia (8 times the odds compared to myopia), but it remains unclear if this relationship is causal. In those with low levels of hyperopia, the odds of anisometropia was 80% lower than children with myopia. In the younger age group, there was no difference in the prevalence of anisometropia across refractive groups.

The prevalence of anisometropia elsewhere in the world varies by location (O'Donoghue *et al*., 2013). For instance, in Australia the prevalence is reported as 1.6% in 6-year-old children (Huynh *et al*., 2006), 6.7% in 4- to 13-year-old American Indians (Dobson *et al*., 2008) and 9.9% in 7- to 18-year-old Taiwanese children (Shih *et al*., 2005).

1.3.2 The burden of refractive error

Concerns over the spiraling rates of myopia around the world are not centred on the inconvenience of refractive error but due to its association with a range of ocular comorbidities including glaucoma, cataract, myopic maculopathy and retinal detachment (Flitcroft, 2012). Nevertheless, myopia is not the only refractive error type that carries a burden of ocular disease and visual impairment. Indeed, both hyperopia and anisometropia have visual

implications in the early stages of life and elevated risk of ocular disease more latterly (Flitcroft, 2012).

1.3.2.1 Clinical implications of hyperopia

While hyperopia appears to have a protective effect for certain types of cataract (Lim *et al*., 1999), having a short AL, the predominant feature in hyperopia (Strang *et al*., 1998), predisposes the individual to other ocular conditions.

Clinicians are alert to the fact that hyperopia carries a risk of angle closure glaucoma (Lowe, 1970; Xu *et al*., 2008). It is also postulated that the link between hyperopia and angle closure glaucoma is greater for Caucasians than those of Asian origin (Congdon *et al*., 1997). Further, it has been shown that AL itself, rather than just a shallow anterior chamber, is important in terms of angle closure risk with an odds ratio of 2.04 per mm reduction in the length of the eye (Casson *et al*., 2009). Despite the association between AL, refractive error itself does not appear to be correlated with risk of angle closure (Casson *et al*., 2009; Senthil *et al*., 2010).

Hyperopes also appear to be prone to certain retinal conditions (Flitcroft, 2012). For instance, eyes with a shorter AL and VCD appear to be anatomically predisposed to both central and branch retinal vein occlusion (Szigeti *et al*., 2015) although findings appear equivocal (Bandello *et al*., 1998; Kir *et al*., 1998). Nevertheless, the more recent work in this area by Szigeti *et al*., 2015 utilised more accurate imaging techniques whereas the outcomes from earlier studies may be obscured by the resolution limitations of applanation ultrasound. Refractive error and AL also seem to have an association with the risk of diabetic retinopathy when considering a broad population-based sample from hyperopia to high myopia (Lim *et al*., 2010). In particular, myopic eyes appear less likely to have diabetic retinopathy, particularly at more severe stages of the disease. In terms of AMD, a meta-analysis showed that in comparison to emmetropes, hyperopes had a 13% higher risk of early disease whereas myopes had a 25% lower risk. Furthermore, each mm increase in AL was associated with a 21% reduction in odds and per-

dioptre move towards hyperopia was linked to a 10% increase in early AMD prevalence (Li *et al*., 2014). In addition to the predisposition to retinal disease, hyperopes also present a greater surgical challenge for routine procedures such as cataract extraction due to the typical shallow nature of the anterior chamber in these patients (Gogate and Wood, 2008). In these eyes, it is more difficult for the surgeon to perform intraocular manipulations and introduce instruments in and out of the eye, which increases the risk of iatrogenic complications.

Of course, outside of its association with the range of ocular comorbidities above, hyperopia is a well-recognised risk factor for the development of amblyopia and strabismus, particularly at moderate to high levels (Ingram, 1977; Ip *et al*., 2008; Klimek *et al*., 2004; Kulp *et al*., 2014). The literature shows that for post-cycloplegic refractive error >+3.25 D, the proportion of 3- to 5-year-old children with amblyopia was 34.5% *versus* 2.8% in those 'without' hyperopia (defined as +3.25 D or less in the most positive meridian). Using the same criteria, strabismus was present in 17.7% of children with hyperopia >+3.25 D compared to just 2.2% in those with a refractive error below this threshold (Kulp *et al*., 2014). For those with +5.00 D of hyperopia or more, levels of amblyopia reached 51.5% compared to 13.2% in children with ametropia between +3.50 D and +4.75 D. Similarly, a greater proportion of strabismus was seen in the higher refractive group (32.9%) than at moderate levels of hyperopia (8.4%) (Kulp *et al*., 2014). Others have outlined the association between hyperopia and esotropia in children aged 6 months to 6 years (Cotter *et al*., 2011; Tarczy-Hornoch *et al*., 2011). Compared with refractive errors between plano and +0.75 D, the odds ratios for esotropia are 23 for hyperopia between +3.00 D and +3.75 D, 59.8 for +4.00 D to +4.75 D and 122 for +5.00 D or more (Cotter *et al*., 2011), which places these children at lifelong risk of unilateral and bilateral reduction in VA (Tarczy-Hornoch *et al*., 2011). Even in the absence of strabismus and amblyopia, impaired visual function at both distance and near is associated with increasing levels of hyperopia in pre-school children (Ciner *et al*., 2021). Furthermore, deficits in measures of attention, visual-motor integration and visual perception are associated with moderate levels (3 D to 6 D) of uncorrected hyperopia in young children (Kulp *et al*., 2017).

1.3.2.2 Clinical implications of anisometropia

While most refractive errors in humans are classified as isoametropic, a minority present with significant interocular differences, which can be deleterious to visual development (Barrett *et al*., 2013; O'Donoghue *et al*., 2013; Flitcroft *et al*., 2020). Anisometropia occurs despite both eyes being exposed to similar environmental influences throughout visual development. Anisometropia and amblyopia are often discovered at the same timepoint through vision screening programmes but it is widely proposed that the former is a precursor and the cause of the latter (Barrett *et al*., 2013). As anisometropia and amblyopia can exist without obvious signs and symptoms, these children typically p establish whether axial eye growth and refractive error could be modified in an isohyperopic cohort by imposing relative hyperopic defocus using MF CLs.resent to clinic some 3 years later than those with strabismus (Ingram, 1977; Shaw *et al*., 1988; Woodruff *et al*., 1994)

Most studies concur that anisometropia exists in around half of all cases of amblyopia in a human population (Robaei *et al*., 2006; Friedman *et al*., 2009; Chia *et al*., 2010; Pai *et al*., 2012). A series of studies have highlighted that a greater proportion of anisometropic amblyopes are anisohyperopes than anisomyopes (Tanlamai and Goss, 1979; Rutstein and Corliss, 1999).

Data from the NICER study reveals that significant differences in VA arise as a consequence of anisometropia with interocular differences in the logarithm of the minimum angle of resolution (LogMAR) acuity of 0.15 for 6- to 7-year-old children and 0.14 at 12 to 13 years of age; this compares to 0.04 and 0.03 for isometropes in the younger and older age groups, respectively (O'Donoghue *et al*., 2013). One study reported that the chance of finding a difference in VA of 2 lines or more was 4.5 times higher in those with 1 D to <2 D of anisometropia compared to children with 0 to <1 D of interocular refractive difference (Tarczy-Hornoch *et al*., 2011). The same authors highlighted a strong linear relationship between the magnitude of anisometropia and prevalence of reduced VA.

Anisometropia coexists with strabismus in around 10% of cases (Friedman *et al*., 2009); some cite figures of 19% (Robaei *et al*., 2006) while others report a link in as many as 28% of cases (Flom and Neumaier, 1966; Flom and Bedell, 1985). Data from the NICER study characterised a cohort of 6- to 7-year-old anisometropes by prevalence of binocular vision status as follows: 92.8% orthophoria; 2.1% esotropia; 1.0% exotropia; and 4.1% heterophoria. In 12- to 13-year-old children, the prevalence rates were similar at 92.2% orthophoria; 2.4% esotropia; 0.8% exotropia; and 4.1% heterophoria (O'Donoghue *et al*., 2013).

A recent study suggests that even small levels of anisometropia can be a marker for impaired regulation of eye growth and subsequent emmetropisation (Flitcroft *et al*., 2020). Data taken from the NICER study for non-amblyopic 6- to 7-year-old children revealed that 71% were isometropes with a MSE interocular difference in refraction of <0.50 D. For those categorised as anisometropes, 29% had a MSE difference of ≥0.50 D, with 6.9% exhibiting an interocular difference of ≥1.00 D and 2.5% with ≥1.50 D. Intriguingly, the refractive error profiles varied between the two groups with the isometropes showing a close to Gaussian distribution whereas anisometropes did not display a normal distribution with a positive skew due to the influence of more hyperopes in this group. Further, among anisometropes, refraction was significantly correlated with CC which was not the case in isometropes. The poor correlation between refraction and CC seen in older children is a marker for emmetropisation; this is due to the fact that CC does not change greatly beyond 2 years of age and as a result achieving emmetropia relies upon the regulation of AL growth to match the optics of the eye. As such, these changes result in a poor correlation between refraction and CC but a strong correlation between corneal radius and AL (Flitcroft *et al*., 2020).

1.3.3 Management of hyperopia

While myopes have a growing armamentarium of options to not only correct, but also to influence, or 'treat', progression of refractive error, hyperopes are not afforded an equivalent

range of options. Indeed, the management of iso- and anisohyperopic refractive error is typically confined to correction with standard optical appliances, namely spectacles and contact lenses (CLs).

The approach to managing hyperopia, that is to say, the magnitude of correction provided relative to the manifest refractive error, or whether a correction should be given at all, is open to conjecture (Mutti, 2007; Cotter, 2007) with scant evidence from randomised studies in humans (Cotter, 2007; Leat, 2011). Correcting hyperopia ≥4.5 D has been suggested due to the increased risk of amblyopia and strabismus at this level of refractive error (Klimek *et al*., 2004). However, some advocate that outside of those with strabismus/amblyopia risk, correcting hyperopia with spectacles may interfere with the emmetropisation process and result in persistence of refractive error (Donahue, 2007); the counter view suggests that correction of the refractive error improves VA and accommodative accuracy and that an optical appliance is unlikely to impede the rapid emmetropisation process that occurs early on in life (Mutti, 2007; Cotter, 2007). Adding to the debate, some report that consistently correcting hyperopia up to the age of about 3 and a half years impedes emmetropisation (Ingram *et al*., 2000); others have shown that by the age of 3 years, there is no difference between those partially corrected or not (Atkinson *et al*., 2000; Atkinson *et al*., 2007). Unsurprisingly, the likelihood of achieving emmetropisation decreases in those with a higher level of hyperopia (Mutti *et al*., 2009). In hyperopic children under the age of 12 years, it has been shown that undercorrection of hyperopia results in a more rapid reduction in refractive error than those with full correction (Yang *et al*., 2014). A recent review considered the effect of prescribing spectacles compared to no intervention for preventing strabismus in infants and children with hyperopia (Jones-Jordan *et al*., 2020). The review concluded that the effect of spectacle correction for prevention of strabismus remains unclear.

The summary of guidelines from the Royal College of Ophthalmologists for the management of amblyopia recommends that ‘significant refractive errors should be corrected’. The guidance

also outlines that consideration should be given to prescribing for degrees of refractive error which have the potential to induce amblyopia even in the presence of normal VA, specifically ≥4.50 of isohyperopia (Royal College of Ophthalmologists, 2006).

Conflicting evidence in the management of hyperopia presents a dilemma for the clinician. Nevertheless, age-dependent guidance on the level of refractive error to correct is available (Leat *et al*., 2011). Furthermore, it is argued that as uncorrected hyperopia in childhood has a negative impact on VA and accommodative accuracy, the reluctance by some to correct hyperopia is unwarranted; this is especially when taking into account that as the course of emmetropisation is largely complete early on in life, the immediate benefits of visual correction may outweigh any concerns regarding interference with this process (Mutti, 2007).

For anisohyperopia specifically, while the mainstay of management is typically refractive correction with spectacles, the benefits of CLs should not be overlooked in these individuals. Using CLs to correct anisohyperopia reduces aniseikonia compared with spectacle lenses and, therefore, maximises the potential for normal binocular vision (Winn *et al*., 1986; Romano and von Noorden, 1999); this is the case for both refractive and axial anisometropes (Winn *et al*., 1988). Further, CLs to correct high levels of anisometropia in children can deliver improvements in VA even after standard amblyopia treatment with spectacles and occlusion therapy has been tried (Roberts and Adams, 2002).

In general, the level of refractive correction for anisohyperopes should aim to fully address any imbalance between the two eyes although, in the absence of accommodative strabismus, a symmetric reduction of up to 1.50 D in spherical correction may be applied (Pediatric Eye Disease Investigator Group, 2002; Repka *et al*., 2003; Holmes *et al*., 2003). The Royal College of Ophthalmologists' guidance suggests that due to the risk of amblyopia, ≥1.50 D of anisohyperopia should be considered for correction (Royal College of Ophthalmologists, 2006).

1.4 Experimental models of refractive error modulation

1.4.1 Background

Much of the evidence about the theories of emmetropisation and refractive error has developed from animal models (Trolio *et al*., 2019; Chakraborty *et al*., 2020). This body of research spans several decades and explores the optical, environmental and biochemical mechanisms in animal models, which has furthered our understanding of the factors that influence eye growth in humans. We know from this extensive work in animals, that visual experience plays a crucial role in guiding ocular growth along a path either towards emmetropisation or refractive error. An overview of the key optical aspects of this work is provided below.

1.4.2 Form deprivation

Experimental models of form deprivation were first described in the seventies where the lids of neonatal monkeys were sutured, which resulted in enlargement of the globe and development of myopia (Wiesel and Raviola, 1977). This work was quickly followed by other form-deprivation experiments using lid suturing method in other species, including tree shrews (Sherman *et al*., 1977), cats (Wilson and Sherman, 1977) and chicks (Wallman *et al*., 1978). Other methods of imposing form deprivation outlined in the literature include opacifying the cornea in newborn macaque monkeys (Wiesel and Raviola, 1979), use of translucent diffusers (Smith, 1998; Smith and Hung, 1999), glue (Wallman *et al*., 1978) and Velcro (Howlett and McFadden, 2006; Ashby *et al*., 2009). Regardless of the method of depriving form, the outcomes from these studies have shown consistently that a sharp retinal image at high contrast is required to permit normal eye growth, otherwise axial myopia will result (Chakraborty *et al*., 2020). Form-deprivation myopia is described as an ‘open-loop’ condition where an absence of visual feedback and a defined refractive endpoint results in an abnormal growth rate of the eye. The magnitude of refractive error, resulting mainly from elongation of the vitreous chamber (Gottlieb *et al*., 1987; Wallman *et al*., 1995; Wildsoet and Wallman, 1995; Troilo *et al*., 2000; Howlett and McFadden, 2006), varies among species. For instance, in

primates, depriving form for 17 weeks results in 5-6 D of myopia (Smith *et al*., 1994; Smith *et al*., 2002), whereas in chicks the rate is much faster with up to 17 D of myopia developing after just 10 days under these conditions (Wallman *et al*., 1995). Despite these varied growth rates between different species, the results unequivocally point towards a common mechanism of ocular growth (Chakraborty *et al*., 2020).

Importantly, the degree of myopia induced by form deprivation is positively correlated to the extent of image degradation with even mild disruption to retinal image quality having the potential to induce a degree myopia (Siegwart and Norton, 1998; Howlett and McFadden, 2006). Across a range of animals, the response to form deprivation decreases with age (Wallman *et al*., 1995; Siegwart and Norton, 1998; Smith *et al*., 1999; Troilo *et al*., 2000;) although a level of plasticity exists even at the end of the initial phase of emmetropisation, at least in chicks (Wallman and Adams, 1987; Papastergiou *et al*., 1998) and monkeys (Smith *et al*., 1999).

Constant exposure to darkness is also sufficient to disrupt normal ocular growth resulting in axial elongation, along with corneal flattening in both chicks (Gottlieb *et al*., 1987; Trolio and Wallman, 1991) and monkeys (Guyton *et al*., 1998). This flattening of the cornea and subsequent loss of corneal power in young animals leads to a more hyperopic refraction.

Common to all animals is the recovery from induced myopia upon cessation of form deprivation (Wallman and Adams, 1987; Wallman *et al*., 1995; Wildsoet and Wallman, 1995; Qiao-Grider *et al*., 2004; Howlett and McFadden, 2006), although the rate varies between species, with recovery within 2 weeks for chicks (Wallman and Adams, 1987) compared with around 8 days for guinea pigs (Howlett and McFadden, 2006) and up to 1366 days for rhesus monkeys (Qiao-Grider *et al*., 2004). A rapid deceleration in eye growth occurs once the period of deprivation has ended, led chiefly by changes to the vitreous chamber and choroid (Wallman *et al*., 1995; Wildsoet and Wallman, 1995). The recovery response to form deprivation is dependent upon

the magnitude of myopia and the age at which the penalisation is ended (Qiao-Grider *et al*., 2004).

Intriguingly, visual deprivation in humans, as a result of conditions such as ptosis (O'Leary and Millodot, 1979), corneal opacity (Gee and Tabbara, 1988) or cataract (von Noorden and Lewis, 1987), is also associated with the development of myopia and is presumed to be due to a similar mechanism observed in animals.

1.4.3 Lens-induced ametropia

Animal studies have shown that the eye is able to compensate for imposed defocus. In other words, ocular growth of the eye adapts in response to a change in focal plane to decrease or eliminate the refractive error; this occurs with both myopic and hyperopic defocus (Schaeffel *et al*., 1988; *Trolio et al*., 2019). When hyperopic defocus is introduced using negative lenses, the eye elongates as the choroid thins which moves the retina backwards resulting in a myopic shift. In the case of myopic defocus, imposed with positive lenses, the opposite response occurs where the choroid thickens, bringing the retina forward, leading to a hyperopic shift in refraction. In both scenarios, the changes are largely due to changes in the vitreous chamber (Wildsoet and Wallman, 1995).

Defocus created using lenses is considered to be a 'closed-loop' condition, where changes to eye growth stop once the imposed refractive error has been compensated for (Morgan *et al*., 2013). As with form deprivation, the changes in response to lens-induced ametropia are observed across a wide range of species including chicks (Irving *et al*., 1992; Wallman *et al*., 1995; Wildsoet and Wallman, 1995), tree shews (Norton *et al*., 2006), monkeys (Hung *et al*., 1995; Smith and Hung, 1999), marmosets (Graham and Judge, 1999) and mice (Tkatchenko *et al*., 2010). Although the broad response is shared across different species, the range of compensatory response varies. For instance, chick eyes are able to compensate for defocus extending from -10 to 20 D (Irving *et al*., 1992), whereas monkeys have a more confined range

of -5 to 8 D (Smith and Hung, 1999; Trolio *et al*., 2009). Interestingly, if the degree of imposed defocus falls outside the operating limits of lens compensation then this results in little to no change in refractive error (Irving *et al*., 1995; Smith and Hung, 1999; Tkatchenko *et al*., 2010). As seen in form deprivation work, when the experimental lens is removed, there is a fast reversal of choroidal thickness, and consequently, AL, to re-establish normal vision (Wallman *et al*., 1995; Wildsoet and Wallman, 1995). It is noteworthy that, in keeping with animal models, imposition of hyperopic and myopic defocus for one to two hours results in bidirectional changes in choroidal thickness and AL in young adult humans (Moderiano *et al*., 2019; Chakraborty *et al*., 2012; Chakraborty *et al*., 2013).

Naturally, as the visual environment changes over time, so too does the dose, magnitude, frequency and sign of defocus. It follows, therefore, that the eye growth response is reliant upon the temporal integration of visual input (Trolio *et al*., 2019; Zhu, 2013). The regulation of ocular growth in response to visual signals over time does not appear to follow a linear path. For example, work in chicks has shown that exposing the eye to alternating periods of hyperopic and myopic defocus over equal blocks of time results in reduced axial growth and subsequent development of hyperopia (Zhu *et al*., 2003; Winawer *et al*., 2005). Other studies in chicks have shown that the response to myopic defocus has greater influence on refractive outcome than hyperopic defocus; this implies that different mechanisms may exist to drive the ocular response to hyperopic and myopic defocus (Zhu *et al*., 2005; Zhu, 2013;). The frequency and duration of exposure, rather than total time, seems important with regards to invoking a response. For instance, multiple periods of brief exposure to defocus across a single day leads to a greater response than a single dose over an equivalent time period, at least in chicks (Winawer and Wallman, 2002). Time of day in relation to exposure also appears to be important, not only in chicks (Nickla *et al*., 2017), but also humans, with work indicating that the eye may be more responsive to a hyperopic defocus, or ‘go’ signal in the morning, and a myopic defocus or ‘stop’ signal later in the day (Moderiano *et al*., 2019).

Current optical approaches for myopia management in contemporary clinical practice include multifocal (MF) CL and orthokeratology (OK), which impose competing hyperopic and myopic defocus signals across large parts of the retina simultaneously (Chakraborty *et al*., 2020). Work in guinea pigs reveals that exposure to dual-focus lenses with alternating power zones produces a response that is equivalent to the mean of the two powers (McFadden *et al*., 2014). In other species (Tse *et al*., 2007; Benavente-Pérez *et al*., 2012a), the response to a dual-focus stimulus seems to have a greater affinity for the positive component of the lens resulting in a hyperopic shift in refraction.

Although form deprivation and hyperopic defocus both lead to axial myopia, the underlying mechanisms may be different. This is highlighted in work where blocking the parasympathetic innervation to the chick eye inhibits form-deprivation myopia but does not impact upon the expected response from lens-induced defocus (Schmid and Wildsoet, 1996). Furthermore, undertaking optic nerve section in chicks, which eliminates active accommodation, results in a 50% greater change in AL driven by form derivation compared to an equivalent level of spatial blur imposed by defocus (Choh *et al*., 2006).

Environmental light levels also appear to impact the response to both form deprivation and lens-induced defocus. Rearing chicks in bright light inhibits myopia development from form deprivation entirely but only has a modest effect on compensation to hyperopic defocus (Ashby and Schaeffel, 2010); a similar outcome is observed in macaques (Smith *et al*., 2012).

The literature on lens-induced ametropia in animals has provided a firm foundation for the development of optical interventions to modulate refractive error in humans, although to date, exclusively in the context of myopia (Beasley *et al*., 2018).

1.4.4 Peripheral defocus

Key findings in chicks have highlighted that eye growth can be guided selectively in areas locally subjected to retinal deprivation (Hodos and Kuenzel, 1984; Wallman *et al*., 1987); a similar response has also been shown to exist in monkeys (Smith *et al*., 2005; Smith *et al*., 2009). In addition to form deprivation, a selective retinal response to localised defocus also occurs in chicks and non-human primates (Diether and Schaeffel, 1997; Morgan and Ambadeniya, 2006; Liu and Wildsoet, 2011; Benavente-Pérez *et al*., 2014) where hemifield exposure to negative and positive defocus results in the local development of myopia and hyperopia, respectively (Diether and Schaeffel, 1997; Smith *et al*., 2010). Peripheral defocus also appears to influence eye growth (Liu and Wildsoet, 2011; Benavente-Pérez A *et al*., 2012; Liu and Wildsoet, 2012; Benavente-Pérez *et al*., 2014). Intriguingly, the response to hyperopic peripheral defocus is less than full field exposure, whereas compensation to myopic peripheral defocus is the same (Morgan and Ambadeniya, 2006), if not greater (Liu and Wildsoet, 2011; Benavente-Pérez *et al*., 2014), than a full field approach. Animal work has shown that to slow eye growth with peripheral myopic defocus, treatment zones need to relatively large (Morgan and Ambadeniya, 2006; Liu and Wildsoet, 2011; Benavente-Pérez *et al*., 2014) compared to the smaller zones of peripheral hyperopic defocus that are required to trigger axial elongation (Smith *et al*., 2009; Benavente-Pérez A *et al*., 2012; Benavente-Pérez *et al*., 2014;). In contrast, some have shown that providing peripheral defocus using lenses with a central hole does not appear to impact central refraction in chicks, implying that peripheral defocus does not necessarily influence refraction measured centrally (Schippert and Schaeffel, 2006).

Historically, it was thought that high foveal sensitivity was particularly important for detecting defocus and subsequent emmetropisation (Chakraborty *et al*., 2020). However, we now understand from work with non-foveated species, such as fish (Shen *et al*., 2005), or those without the ability to process at high spatial resolution (Sherman *et al*., 1977; Wallman *et al*., 1995; Howlett and McFadden, 2006) that foveal input may not be critical. Work with rhesus monkeys supports this hypothesis, where despite having undergone foveal ablation, normal

emmetropisation was achieved along with compensation for form deprivation (Smith *et al*., 2007). Also, it seems that foveal input is not essential for compensation to defocus, as chicks (Wildsoet and Schmid, 2000) and monkeys (Smith *et al*., 2005) are able to recover from induced refractions in the absence of a central signal. The fact that the eye responds at a local and regional retinal level, rather than being reliant upon a central, neural mechanism, has paved the way for refractive modulation approaches in humans.

As peripheral defocus has the ability to influence refraction, it follows that this would be expected to be accompanied by corresponding eye growth. In humans, the characteristics of peripheral refraction are linked to central refraction. Specifically, myopes have a tendency to be relatively hyperopic along the horizontal axis, whereas hyperopes tend to exhibit relative peripheral myopia (Millodot, 1981; Mutti *et al*., 2000). There is conjecture as to whether these respective peripheral profiles are the cause or the result of central refractive development (Seidemann *et al*., 2002). We have learnt from work with monkeys that exposure to form deprivation leads to relative peripheral hyperopia (RPH) which increases with the magnitude of central myopia (Huang *et al*., 2009). The extent of peripheral refraction asymmetry varies with eccentricity in marmosets as does the strength of the relationship between central and peripheral refraction (Totonellly *et al*., 2006; Benavente-Pérez *et al*., 2012b; Benavente-Pérez *et al*., 2014). In addition to the shift towards relative hyperopia as the eye grows, in marmosets it appears that there is a move towards relative peripheral myopia during periods of slower growth during emmetropisation (Benavente-Pérez *et al*., 2016).

The temporal aspects of visually driven eye growth and its interaction with peripheral refraction have also been considered in marmosets (Benavente-Pérez *et al*., 2016). This work has shown that baseline measures of peripheral refraction can only predict the compensatory changes to negative defocus in combination with central refraction, or once the eyes have started to compensate for the imposed status (Benavente-Pérez *et al*., 2016). The collective evidence in this area provides an understanding of the relationship between peripheral refractive

asymmetry and the visual experience of the central retina (Benavente-Pérez *et al*., 2012a; Benavente-Pérez *et al*., 2012b; Benavente-Pérez *et al*., 2014;). The fact that peripheral refraction appears to be both a cause and an effect of eye growth, points towards its role in the progression of myopia, and perhaps most significantly, opportunities to develop interventions to control it (Chakraborty *et al*., 2020).

1.4.5 Ocular shape

Ocular shape in humans varies according to refractive subtype with myopic eyes typically having a steeper, or relatively prolate, profile whereas emmetropes and hyperopes have a flatter, or oblate, retinal shape (; Atchison *et al*., 2005; Gilmartin *et al*., 2005; Charman and Radhakrishnan, 2010; Atchison and Charman, 2011; Schmid, 2011; Verkicharla *et al*., 2012). Techniques such as magnetic resonance imaging (MRI) have been used to show the link between ocular shape and peripheral refraction with the relatively more prolate myopic eye exhibiting RPH (see Figure 1.3). Conversely, the oblate profiles seen in emmetropes and hyperopes are associated with a relatively myopic peripheral refraction (Atchison *et al*., 2005; Gilmartin *et al*., 2005; Charman and Radhakrishnan, 2010; Atchison and Charman, 2011; Schmid, 2011; Verkicharla *et al*., 2012) (see Figure 1.4).

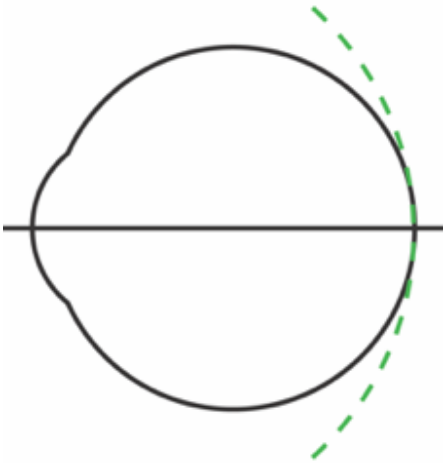

Figure 1.3 Relatively prolate ocular shape in myopia with corresponding retinal image shell, indicated by the green dashed line, demonstrating RPH

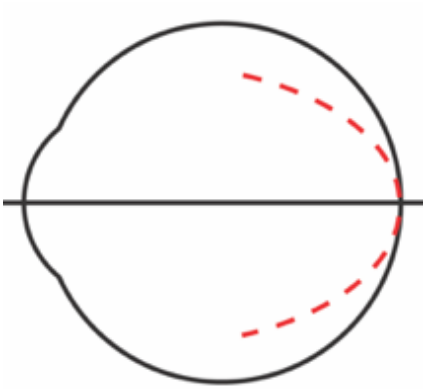

Figure 1.4 Relatively oblate ocular shape in hyperopia with corresponding retinal image shell, indicated by the red dashed line, demonstrating relative peripheral myopia

MRI studies in infant rhesus monkeys (Huang *et al*., 2009; Smith *et al*., 2013) and marmosets (Totonelly and Trolio, 2008) with specific parts of the visual field targeted by form deprivation or defocus reveal that changes in peripheral refraction correspond to vitreous chamber shape changes. A limited number of human studies have explored peripheral refraction and retinal shape in combination and where these have been undertaken, the emphasis has been in relation to myopia. It has been shown, using partial coherence interferometry (PCI), that peripheral refraction, peripheral AL and retinal profile are affected by race, meridian and refraction (Verkicharla *et al*., 2016; Verkicharla *et al*., 2017). East Asians have a more prolate retinal shape and exhibit a greater degree of RPH than Caucasians with a steeper profile along the horizontal meridian compared to the vertical meridian.

Although many contemporary clinical approaches to arrest myopia progression centre on manipulation of peripheral hyperopic defocus, the role of retinal shape in the pathogenesis of myopia is yet to be fully established (Chakraborty *et al*., 2020). Indeed, there is evidence among both Caucasian and Chinese cohorts which show that peripheral hyperopic defocus may not predict the development, nor the progression of myopia (Sng *et al*., 2011a; Sng *et al*., 2011b; Mutti *et al*., 2011; Lee and Cho, 2013; Atchison *et al*., 2015; Atchison and Rosén, 2016; Rotolo *et al*., 2017; Mutti *et al*., 2019). The findings from this body of work highlight that the interaction between peripheral refraction and myopia is far from straightforward and that a number of optical factors are at play. Nevertheless, as retinal shape is related to peripheral

defocus it may play an important role in driving the development and progression of myopia in humans.

1.4.6 Accommodation

Given that accommodation is driven by various cues, including retinal defocus, chromatic aberration and optical vergence (Kruger *et al*., 1993; Del Aguila-Carrasco *et al*., 2017), it has been identified as a potential factor in the development of myopia. Although animal work indicates that emmetropisation is guided by retinal defocus, it is unclear whether accommodation-related defocus has a part to play in this process (Chakraborty *et al*., 2020). Evidence drawn from chicks (Schaeffel *et al*., 1988; Ostrin *et al*., 2011), marmosets (Clarke *et al*., 1985) and rhesus monkeys (Croft *et al*., 1998; Ostrin and Glasser, 2010) has demonstrated the presence of active accommodation and explored its influence with regard to ocular growth. As in humans, accommodation in primates is driven by the crystalline lens, whereas in chicks the cornea is also involved in the process (Troilo and Wallman, 1991; Glasser *et al*., 1994; Glasser *et al*., 1995). Accommodative lag (Mutti *et al*., 2006), accommodative microfluctuations (Day *et al*., 2009), tonic accommodation (McBrien and Millodot, 1987; Gwiazda *et al*., 1995) and interpretation of blur (Gwiazda *et al*., 1993) have all been implicated in the process of emmetropisation and myopia development. Early work suggested that the accommodative response to induced hyperopic defocus using negative lenses provided a signal for eye growth (Schaeffel *et al*., 1988). Use of atropine, a muscarinic antagonist has shown a protective effect for myopia progression in animal models and was thought at the time to relate to the cycloplegic effect on the ciliary muscle (Young, 1965). However, subsequent work has shown that the mechanism of atropine in the context of myopia control is not attributable to accommodation.

The cues to accommodation begin at a retinal level with afferent signals transmitted by the optic nerve for higher level processing. The efferent signals pass from the Edinger-Westphal nucleus *en route* to the ciliary ganglion and then to the ciliary muscle *via* the ciliary nerves

(Crawford *et al*., 1989). Signals arising from the Edinger-Westphal nucleus, situated in the midbrain, kickstarts a binocular and consensual accommodative response. It has been discovered from animal work that disruption of the afferent or efferent components of the pathway does not stop the development of myopia in response to lens-induced defocus (Schaeffel *et al*., 1990). It seems that ocular growth proceeds, led by visual cues, even in the absence of active accommodation as demonstrated in rhesus monkeys with optic nerve section (Raviola and Wiesel, 1990), along with ciliary nerve section (Schmid and Wildsoet, 1996) and destruction of the Edinger-Westphal nucleus (Schaeffel *et al*., 1990) in chicks. Further, it has also been shown that atropine in chicks reduces experimental myopia but given this drug has no effect on the striated ciliary muscle in these animals, the findings point towards a non-accommodative mechanism (McBrien *et al*., 1993). In addition, local growth of the eye is influenced by defocus applied regionally; this does not support the theory that accommodation is responsible for the modulation of eye growth given that accommodative effort changes focus in a uniform manner across the visual field (Diether and Schaeffel, 1997). Taken together, these findings indicate that a local mechanism within the eye is responsible for eye growth control (Chakraborty *et al*., 2020). However, the findings above do not entirely exclude accommodation as a factor in the process of refractive modulation given its link with retinal defocus (Charman, 1999). Allowing brief intervals of clear vision between periods of hyperopic defocus impedes the development of experimental myopia in a range of species (Schmid and Wildsoet, 1996; Shaikh *et al*., 1999; Kee *et al*., 2007). The outcome from this work suggests that if it is possible to compensate for induced defocus by accommodating, a similar myopia inhibitory effect should occur. With this in mind, a high lag of accommodation would be expected to provide a stimulus to the eye to grow from the resultant hyperopic defocus (Chakraborty *et al*., 2020). Efforts to explore this hypothesis have looked at the characteristics of accommodation in marmosets before and after experimental myopia has been induced (Troilo *et al*., 2007). The outcome showed that accommodative lag increased after lens-induced myopia occurred suggesting this was a consequence rather than a cause of this refractive change. The findings also showed that accommodative performance prior to

induced defocus was unable to predict the extent of myopia development, a result that is supported by additional work in chicks (Aleman and Schaeffel, 2018). Others have evaluated how accommodation affects the ability of chicks to decode focusing errors (Diether and Wildsoet, 2005). A key outcome revealed that disabling accommodative function through ciliary nerve section results in impaired ability to decode and compensate for imposed defocus. In particular, when presented with simultaneous hyperopic and myopic signals, the growth response is biased towards myopia. This work led to the conclusion that accommodation appears to play a part in decoding defocus during the process of emmetropisation. Nevertheless, when all this research is considered in tandem, it is clear that a complex process exists in relationship to accommodation and emmetropisation with multiple pathways at play.

The research undertaken in animals and the role of accommodation has helped to drive the evidence base for humans. Research into the potential link between accommodative lag and myopia in children have been spurred on by the work in animals showing that hyperopic defocus leads to myopia development. However, the outcomes in this area are equivocal with some reporting that increased lags are in place prior to the onset of myopia (Goss, 1991; Drobe and de Saint-André, 1995; Gwiazda *et al*., 2005) whereas others assert that higher levels of lag arise *after* myopia development (Mutti *et al*., 2006). Although in animals, myopic defocus slows or stops myopia development, adopting this rationale to control progression in children using bifocal (BF) and MF spectacle lenses has shown mixed outcomes, achieving little (Shih *et al*., 2001; Edwards *et al*., 2002) to modest success (Leung and Brown, 1999; Gwiazda *et al*., 2003). More recently, research using BF and MF CLs (Anstice and Phillips, 2011; Lam *et al*., 2014; Pauné *et al*., 2015; Walline, 2016; Aller *et al*., 2016; Li *et al*., 2017; Chamberlain *et al*., 2019) have achieved more impressive results in slowing the progression of myopia, although it remains unclear if this is due to the impact of accommodation, peripheral defocus, or a combination of factors. Indeed, a recent appraisal of the current evidence does not point towards a role for binocular vison and accommodation in the development and progression of myopia (Logan *et al*., 2021).

1.4.7 High order aberrations

Although low order aberrations (LOAs) are given prominence when considering the optical characteristics of the eye, monochromatic high order aberrations (HOAs) should not be overlooked as they can degrade the quality of the retinal image and may contribute to refractive error development (Chakraborty *et al*., 2020). It is thought that HOAs, alongside those of low order, can influence depth of focus with a subsequent impact upon ocular development (Charman, 1991; Charman, 2005).

Animal work has allowed fundamental understanding of the changes in HOAs that arise during emmetropisation and the role they play in leading to refractive errors. In particular, the literature shows that in chicks (García de la Cera *et al*., 2006), marmosets (Coletta *et al*., 2010) and monkeys (Ramamirtham *et al*., 2006) HOAs reduce with age due to structural changes to the cornea and lens, findings that are mirrored in humans (Brunette *et al*., 2003). The outcomes from these studies conclude that HOAs contribute relatively little to the improvements in spatial vision and CS that occur during development. Further, it is thought that HOA reduction is a passive process without significant influence from the visual environment (Artal *et al*., 2001). The association between induced ametropias and HOAs have also been explored in a range of species including chicks (García de la Cera *et al*., 2006; Kisilak *et al*., 2006) and monkeys (Ramamirtham *et al*., 2007). Results from this work show that experimental myopia, induced by form deprivation and exposure to hyperopic defocus, are associated with increased levels of HOAs. Interspecies variation exists with ametropias in monkeys linked to higher levels of positive spherical aberration (+SA), whereas in chicks, an increase in negative spherical aberration occurs. The optical shifts that arise during these experimental conditions are thought to be a result of curvature and refractive index changes to the optical structures within the eye as well as changes to the crystalline lens position with respect to the cornea (Ramamirtham *et al*., 2007). It is also noteworthy that myopia is associated with greater levels of +SA in humans (Llorente *et al*., 2004). Importantly, it has been shown that increased HOAs

have been strongly correlated with the degree of LOAs and axial refractive error in hyperopic and myopic monkeys, which implies they arise as a consequence, rather than a cause of ametropia (Ramamirtham *et al*., 2007).

In humans with normal healthy eyes, spherical aberration, coma and trefoil are the key HOAs. Nevertheless, the type and amount of HOAs varies significantly between individuals (Charman, 1991; Thibos *et al*., 2002; Castejón-Mochón *et al*., 2002). The role that HOAs play in the development of refractive error, in humans and animals, remains unclear. Some suggest that spherical aberration and coma in particular are associated with myopia (He *et al*., 2002; Paquin *et al*., 2002) whereas others have found no significant change in HOAs with myopia (Carkeet *et al*., 2002; Cheng *et al*., 2003; Atchison *et al*., 2006). The picture is clouded further by the influence of accommodation which results in dynamic changes to both HOA and LOAs (Lopez-Gil *et al*., 1998; Vilupuru *et al*., 2004). Further longitudinal studies are required to clarify the potential role of HOAs in driving emmetropisation and refractive error (Chakraborty *et al*., 2020).

1.4.8 Spectral and temporal light characteristics

In addition to monochromatic aberrations, the influence of other factors on ocular growth and development, such as longitudinal chromatic aberration (LCA), wavelength, intensity and duration of exposure need consideration.

Evidence from work in guinea pigs (Liu *et al*., 2011) and chicks (Rucker and Wallman, 2009) indicates that the eye uses LCA to help steer axial growth and refraction. As LCA results in long wavelengths of light to be focused in a more hyperopic plane than short wavelengths of light, the eye's refractive state is relatively hyperopic for long-wavelength light. Colour fringes that arise from broadband light, which are component parts of the retinal image, provide cues to the nature of defocus, that is to say, hyperopic or myopic (Rucker, 2013). Although the literature highlights that LCA can provide a directional signal for accommodation in humans,

its role in the process of emmetropisation remains uncertain (Kruger *et al*., 1993; Seidemann and Schaeffel, 2002). Detection of LCA relies upon the presence of short, medium and long wavelength cones (Gisbert and Schaeffel, 2018); however, in humans, short-wavelength cones are more scarce than medium and long wavelength variants (Roorda and Williams, 1999). It has been shown from electrophysiological research that the sensitivity of short-wavelength cones is reduced in myopia (Kawabata *et al*., 1996; Yamamoto *et al*., 1997) while others suggest that retinal ganglion cells, which have high sensitivity to short-wavelength light may offer a spectral tuning mechanism to differentiate between long and short wavelengths of light (Gamlin *et al*., 2007).

In animals, the spectral influences of light upon eye growth appear to be species dependent. In fish (Kröger and Wagner, 1996), chicks (Seidemann and Schaeffel, 2002; Foulds *et al*., 2013; Torii *et al*., 2017) and guinea pigs (Liu *et al*., 2011; Jiang *et al*., 2014), eyes become less myopic when reared under short-wavelength light compared to those exposed to long-wavelength light. In the short-term, the direction and extent of growth match the model predictions; however, growth rates under these conditions for a longer period exceed the expected outcome suggesting that a more complex process is at play (Seidemann and Schaeffel, 2002; Rucker and Osorio, 2008). One hypothesis proposes that blue light may be responsible for preferential stimulation of the 'ON' pathway to inhibit myopia progression (Jiang *et al*., 2014). In contrast to the species above, non-human primates raised under long-wavelength light exhibit decreased eye growth (Hung *et al*., 2018); this finding is supported by work showing that rhesus monkeys exposed to conditions predominated by long-wavelength light demonstrate slowed eye growth (Smith *et al*., 2015). In tree shrews, exposure to red (long-wavelength) light results in hyperopia (Gawne *et al*., 2017a), whereas myopia occurs under conditions of short-wavelength light (Gawne *et al*., 2017b) even in the presence of defocus. In other words, the chromatic signals dictated the direction of eye growth to an extent where the defocus conditions were largely ignored. In particular, even when exposed to hyperopic

defocus, with expectation that myopia would follow, the animals remained relatively hyperopic. The underlying reasons for these outcomes remain obscure (Chakraborty *et al*., 2020).

A selection of studies has shown that the status of ambient lighting also has a role in regulating eye growth with increased levels having a protective effect against myopia under conditions of form deprivation (Cohen *et al*., 2011; Smith *et al*., 2012; Chen *et al*., 2017). The findings here may align to work showing that time outdoors can curb myopia development in children (Xiong *et al*., 2017; Morgan *et al*., 2021; Wolffsohn *et al*., 2021). The underlying mechanisms relating to these protective effects are yet to be established but neurochemical factors, such as melanopsin and dopamine, have been implicated (Ashby and Schaeffel, 2010; Ostrin, 2018; Flanagan *et al*., 2020). In an outdoor setting, light levels range from 1000 lux under cloudy conditions to 150,000 lux on a bright day (Ostrin, 2017) with a broad spectral composition. With this in mind, it is difficult to pinpoint if the protective effects of time outdoors in relation to myopia can be attributed to a specific region of the spectrum. The situation is complicated by the fact that greater time outdoors reduces the potential for accommodation-related defocus experienced during near tasks in an indoor environment.

1.4.9 Summary

The extensive body of work on animals outlined here affirms the role of the visual environment in guiding refractive state by mediating eye growth. The vast range of studies have furthered our understanding of the process of emmetropisation and refractive error development in humans. Taken together, the outcomes demonstrate that several cues exist to allow the eye to modulate its growth during emmetropisation. In particular, visual signals provided by accommodation, peripheral defocus, HOAs and chromatic aberrations, serve to direct the sign and magnitude of retinal defocus and ultimately drive refractive development.

1.5 Optical interventions for refractive error modulation in humans

1.5.1 Background

Here, optical interventions for modulating refractive error in humans will be considered. It is striking that this entire body work relates exclusively to the realm of myopia. As such, it may be more appropriate to consider this section as a summary of 'lessons from myopia', which provides an opportunity to ponder if, and how, these approaches could be applied to a hyperopic cohort.

1.5.2 Undercorrection of myopia

As outlined earlier (see section 1.4.3), it has been shown in animals that myopic defocus can inhibit axial growth during development (Schaeffel *et al*., 1988; Wildsoet and Wallman, 1995 *Trolio et al*., 2019). The overarching outcome from these studies has led practitioners to purposefully avoid fully correcting myopia for distance vision (DV) in an attempt to slow the progression of refractive error (Tang *et al*., 2020). As close work and accommodation have been implicated as possible factors that lead to the development of, and drive, the progression of myopia, the rationale was that undercorrection of the refractive error would reduce accommodative demand and exert some influence over the outcome.

In contrast to the findings in animal studies, evidence from two clinical studies in humans has revealed that undercorrection *accelerates* the development and progression of myopia (Chung *et al*., 2002; Adler and Millodot, 2006). In particular, a randomised trial has shown that undercorrection of refractive error rendering the child unable to see beyond 6/12 leads to a mean myopic progression of 1.00 D over two years *versus* 0.77 D in those receiving full correction (Chung *et al*., 2002). The findings from this study are mirrored in a retrospective review of clinical data, once again showing that undercorrection of myopia leads to greater levels of progression (Adler and Millodot, 2006). However, the outcomes here are contested by evidence from a study reporting that children with no refractive correction showed slower

progression and less axial growth than those given full correction, by a magnitude of 0.27 D over 2 years (Sun *et al*., 2017). Despite the equivocal findings from this work, the argument for undercorrection of myopia to prevent progression, remains unconvincing (Tang *et al*., 2020; Logan and Wolffsohn, 2020; Jonas *et al*., 2021).

1.5.3 Spectacle lens correction

Over the past 20 years, numerous studies have explored the effect of BF, MF and progressive addition lenses (PALs) on the progression of myopia (see Table 1.2). The general rationale for these approaches is to allow the wearer to utilise the top part of the spectacle lens to see clearly in the distance through full refractive correction, with the addition power in the bottom part of the lens designed to reduce accommodative effort and lag.

Study	Duration	Details	Cohort	Intervention	*Effect
Fulk *et al*., 2000	2.5 years	Randomised, masked	6-13 years	SV (n = 40) BF 1.50 D add (n = 42)	0.25 D (20%)
Edwards *et al*., 2002	2 years	Randomised, double masked	7-10.5 years Chinese	SV (n = 132) PAL 1.50 D add (n = 121)	0.14 D (11%)
Gwiazda *et al*., 2003	3 years	Randomised, masked	6-11 years	SV (n = 233) PAL 2.00 D add (n = 229)	0.20 D (14%)
Yang *et al*., 2009	2 years	Randomised, masked	7-13 years Chinese	SV (n = 75) PAL 1.50 D add (n = 74)	0.26 D (17%)
COMET2, 2011	3 years	Randomised, masked, multicentre	8-12 years	SV (n = 58) PAL 2.00 D add (n = 52)	0.28 D (24%)
Sankaridurg *et al*., 2010	1 year	Randomised	6-16 years Chinese	Type I, Type III, SV (n = 50 per group Type II (n = 60)	**0.29 D (30%)
Berntsen *et al*., 2012	1 year	Randomised, masked	6-11 years	SV (n = 42) PAL 2.00 D add (n = 41)	0.18 D (35%)
Hasebe *et al*., 2014	1.5 years	Randomised, masked, cross-over	6-12 years Japanese	SV (n = 44) PAL 1.50 D add (n = 42)	Phase 1: 0.31 D (18%) Phase 2: 0.02 D (2%)
Cheng *et al*., 2014	3 years	Randomised, masked	8-13 years Chinese	SV (n = 41) BF 1.50 D add (n = 48) PBF 1.50 D add 3 Δ base in (n = 48)	BF: 0.81 D (39%) PBF: 1.05 D (51%)
Lam *et al*., 2019	2 years	Randomised, masked	8-13 years Chinese	SV (n = 90) DIMS (n = 93)	0.44 D (52%)

Table 1.2 Summary of myopia control studies using spectacle lens correction with single vision (SV), BF/prismatic bifocal (PBF), PALs and defocus incorporated multiple segments (DIMS). Adapted from Tang *et al*., 2020. *Dioptric treatment effect in slowing myopia progression over study period. ** In a subgroup of children (with myopic parents) using Type III lenses.

For PALs, the studies (COMET2, 2001; Edwards *et al*., 2002; Gwiazda *et al*., 2003; Yang *et al*., 2009; Berntsen *et al*., 2012; Hasebe *et al*., 2014) point towards an insignificant effect of myopia retardation overall although children with esophoria and accommodative lag may benefit from a greater effect (Tang *et al*., 2020).

For BF spectacle lenses, an early study showed that a 1.50 D add slowed progression of myopia in children with near-point esophoria by 20% compared to SV lenses, which equated to 0.25 D over 30 months (Fulk *et al*., 2000). A more recent study has shown that executive BFs both with and without base in prism can exert control on progression of myopia in fast progressors, particularly for those with a low accommodative lag (Cheng *et al*., 2014). Although the inclusion of base in prism to reduce fusional vergence achieved a greater dioptric effect than lenses without prism, AL length changes were similar for both lens types.

A more complex paradigm was explored in a study using 3 bespoke lens designs aimed at reducing relative peripheral hyperopic defocus (RPHD) in myopes (Sankaridurg *et al*., 2010). Only one type of lens design managed to achieve a meaningful effect of 30% reduction in progression compared to SV lenses in a subgroup of younger participants aged 6 to 12 years whose parents were both myopic. This 'Type III' lens had an asymmetrical design with a central clear aperture with positive additional power in the horizontal meridian, optimised to reduce astigmatism in that meridian. The other, ineffective lens variants consisted of rotationally symmetric designs each with differing amounts of positive peripheral power surrounding a clear central aperture.

A recent novel design termed DIMS has shown more promise as a myopia control spectacle lens option (Lam *et al*., 2019; Jonas *et al*., 2021). The DIMS lens offers simultaneous vision

with a central optic zone which provides full refractive correction, surrounded by multiple segments which deliver constant myopic defocus of +3.50 D. Initial results from the 2-year clinical trial have shown that children wearing the experimental design had 52% less myopic progression and 62% less axial growth than SV controls. Recently, follow up results have shown that the myopia control effect was sustained in the third year for children who had used the DIMS in the original 2 years of the study and was also shown in children switching from SV lenses during the first 2 years of the study to the DIMS lens in the third year (Lam *et al*., 2021).

1.5.4 CL correction

The following sections outline the attempts to arrest the progression of myopia through use of various CL designs.

1.5.4.1 Rigid gas permeable (RGP) CLs

Several studies have considered the impact of daytime wear of RGP CLs on myopia progression. Outcomes from early work in this area were limited by study design, such as lack of randomisation or participant age criteria being outside the expected range of likely progression (Stone, 1976; Perrigin *et al*., 1990; Khoo *et al*., 1999). Nevertheless, two randomised clinical trials (Walline *et al*., 2004; Katz *et al*., 2003) have shown that RGP CLs do not appear to influence axial growth, although one of the studies did report slower progression of myopia in participants wearing RGP CLs *versus* those wearing soft CL (Walline *et al*., 2004). It is thought that the effect of RGP CLs on the refractive outcome in this study occurred at a corneal level and that any apparent retardation of myopia was likely to be transient. Taking all of the above into account, daytime wear of RGP CLs is not considered to be a credible approach for myopia control.

1.5.4.2 Soft CLs

BF and MF soft CLs have become increasingly popular interventions to attempt to control myopia progression in children (Wolffsohn *et al*., 2021). The ease of adaptation, along with the cosmetic and practical advantages that soft CLs offer, make them an attractive option for the patient. For the practitioner, having a simple fitting approach without the need for specialist equipment makes soft CLs an accessible entry point into myopia management. Numerous studies have explored the efficacy of BF and MF CLs, the outcomes from which are summarised in Table 1.3.

Study	Duration	Details	Cohort	Intervention	*Effect
Anstice and Phillips, 2011	20 months	Randomised, paired eye control, cross-over	11-14 years	DF 2.00 D add (n = 40) SV (n = 40)	0-10 months: 0.25 D (37%) 11-20 months: 0.20 D (54%)
Sankaridurg *et al*., 2011	12 months	Randomised	7-14 years Chinese	RPH CL (n = 45) SV (n = 40)	0.29 D (34%)
Walline *et al*., 2013	24 months	Matched study	8-11 years	Proclear multifocal 2.00 D add (n = 40) SVCL (n = 40)	0.52 D (50%)
Lam *et al*., 2014	24 months	Randomised, double masked	8-13 years Chinese	DISC 2.5 D add (n = 65) SVCL (n = 63)	0.21 D (25%) 0.44 D (50%) > 6 h 0.54 D (58%) > 7 h 0.53 D (60%) > 8 h
Pauné *et al*., 2015	24 months	Prospective, non-randomised	9-16 years Caucasian	SRRG (n = 30) OK (n = 29) SV (n = 41)	0.42 (43%)
Aller *et al*., 2016	12 months	Randomised, masked	8-18 years	BFSCL (n = 39) SVCL (n = 40)	0.57 D (72% in those with eso fixation disparity)
Cheng *et al*., 2016	12 months	Randomised, double masked	8-11 years	+SA (n = 64) SVCL (n = 63)	0-6 months: 0.21 D (54%) At 12 months: 0.14 D (20%)
Chamberlain *et al*., 2019a	36 months	Randomised, double masked	8-12 years	DF 2.00 D add (n = 70) SVCL (n = 74)	0.73 (59%)
Ruiz-Pomeda *et al*., 2018	24 months	Randomised, double masked	8-12 years	DF 2.00 D add (n = 46) SVCL (n = 33)	0.29 (39%)

Table 1.3 Summary of myopia control studies using soft BF and MF CLs comparing: SV CL; dual focus (DF); reduction of RPH design; SV spectacle lens; defocus incorporated soft CL (DISC); soft radial refractive gradient (SRRG) CL; OK; bifocal soft CL (BFSCL); and soft CL

with +SA. Adapted from Tang *et al*., 2020. *Dioptric treatment effect in slowing myopia progression over study period.

For soft BF CLs, there are broadly two approaches taken in the attempt to control progression of myopia. In both scenarios, the CL design consists of a central distance zone providing full correction of myopia. However, the guiding principle of one design is to have a peripheral annulus of relative positive power around the central zone to reduce peripheral hyperopic defocus (see Figure 1.5). The second design, often termed 'DF', also exposes the eye to myopic defocus in the periphery but in this case the design consists of concentric rings which alternate between full distance correction and relative positive power (see Figure 1.6).

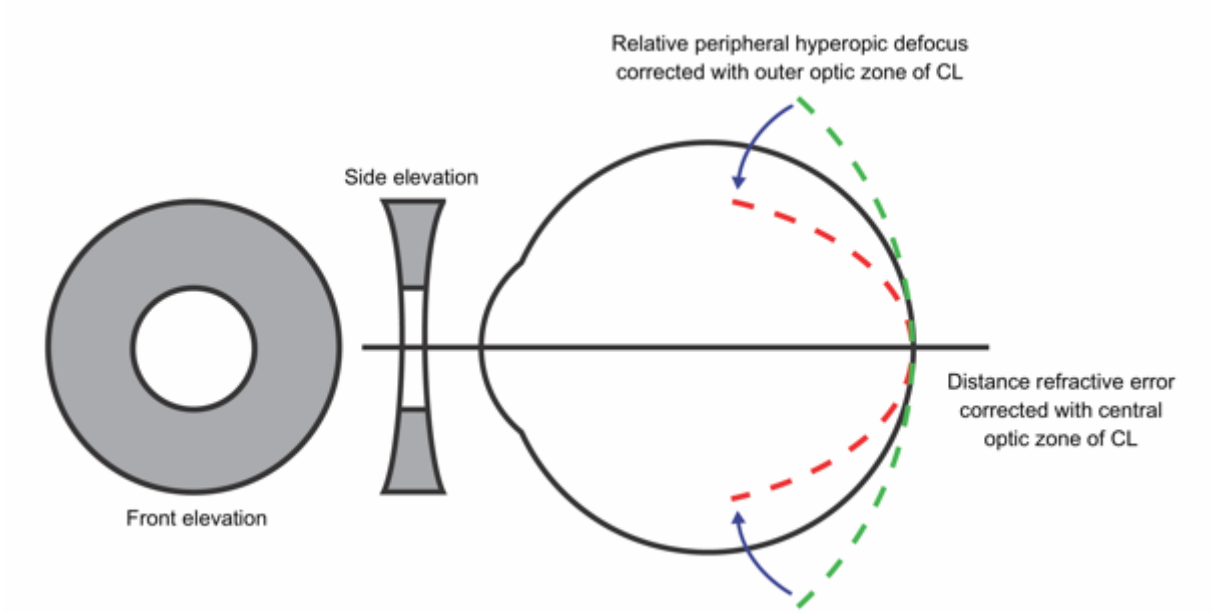

Figure 1.5 RPHD corrected with a centre-distance BF CL while full refractive error is corrected centrally

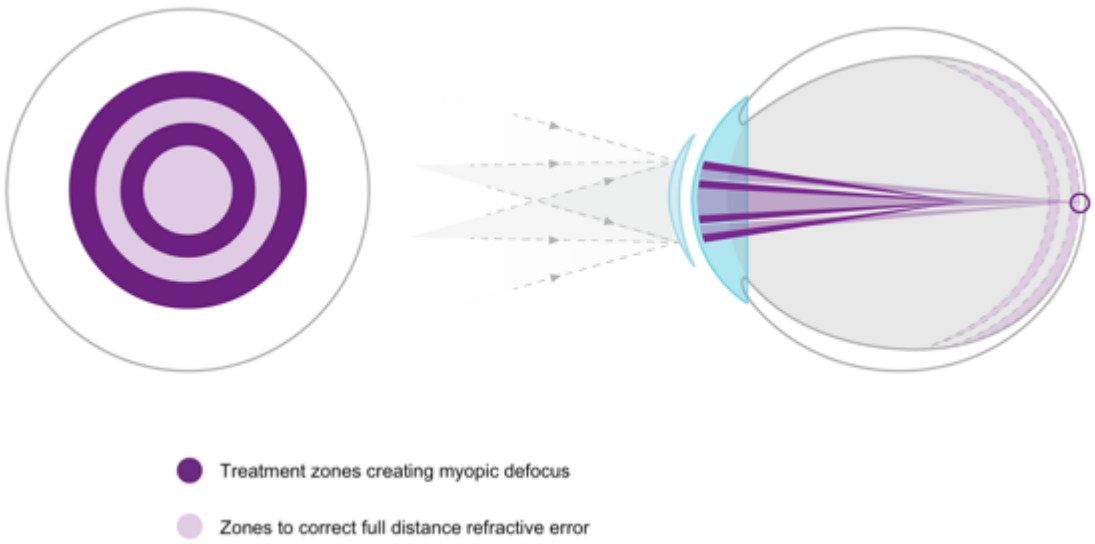

Figure 1.6 DF CL with central distance zone and alternating concentric zones of myopic defocus and full refractive error correction

Other lens designs exist which also target reduction of RPH. For instance, a novel soft lens design with a clear central zone surrounded by an annulus that increases in relative positive power towards the periphery, has been reported to achieve 34% less progression in refractive error and an estimated 33% slowing in axial growth compared to spectacle wearers over a 12-month period (Sankaridurg *et al*., 2011). Impressive results from a randomised, masked study showed a 72% slowing of myopia progression using a BF CL compared to SV CLs, although this effect was limited to children with eso fixation disparities at near (Aller *et al*., 2016). The addition of the Vistakon Acuvue Bifocal (Johnson & Johnson, Vision) used in the study was selected to neutralise the associated phoria in each participant.

A study, using a soft, centre-distance, MF CLs intended for presbyopes, the Proclear multifocal (CooperVision), reported a 50% reduction in myopia progression along with 29% less axial elongation over a 2-year period (Walline *et al*., 2013). In further work, a SRRG design was utilised to correct central refraction while exposing the eye to myopic defocus that gradually increased with eccentricity; this intervention resulted in retardation of myopia progression over

a 2-year period of 43% with 27% less axial growth than SV spectacle-wearing controls (Pauné *et al*., 2015).

CL designs incorporating +SA have also been considered based upon the observation that myopic children with higher levels of +SA demonstrate slower eye growth (Hiraoka *et al*., 2017; Lau *et al*., 2018). A unique lens incorporating +SA into the design to reduce RPH showed a slowing in axial growth compared to controls, although this did not translate into sustained refractive error control at the 12-month timepoint (Cheng *et al*., 2016).

A paired eye control, cross-over trial investigated the use of an experimental concentric BF, or DF soft CL, which provided 2.00 D of myopic defocus (Anstice and Philips, 2011). Participants were assigned randomly to have the intervention in one eye and a SV CL in the fellow eye for 10 months with the lens types then switched over for a further 10 months. In the first 10 months, the intervention lens resulted in a 37% slowing of myopia progression compared to the control condition; axial growth in the intervention eye was almost half the rate of the fellow eye. Following cross-over, the outcome achieved in the second period showed a reduction of 54% in refractive change and 80% in axial growth in the intervention eye *versus* the control eye.

A novel design, termed the defocus incorporated soft CL (DISC) with 2.50 D of myopic defocus reported impressive dose-dependent results achieving a slowing of myopia progression of 50%, 58% and 60% for children wearing the intervention for >6, >7 and >8 hours, respectively (Lam *et al*., 2014). AL changes were consistent with the refractive findings, although precise dose-dependent values for this outcome measure were not reported.

Data from 'Part 1' of a multicentre, randomised, double masked trial using a DF, daily disposable soft lens showed a slowing in myopia progression and axial elongation by 59% and 52%, respectively, over a 3-year period compared to children wearing SV CLs (Chamberlain *et al*., 2019a). The lens is available commercially in various parts of the world as MiSight

(CooperVision). Part 2 of the study was initiated at the 3-year point where children in the control arm of the study were refitted with the intervention lens; these participants were tracked separately from children who had worn the DF lens from the outset. Results after 5 years showed that children from the original control group matched the performance of those wearing the intervention lens from the beginning of the study in terms of refractive error change and axial growth (Chamberlain *et al*., 2019b). A recent update has revealed that 23% of eyes after 6 years of intervention displayed a total MSE refractive change of less than -0.25 D (Chamberlain *et al*., 2020). Another study in Spain also investigated the efficacy of the MiSight CL and showed a 39% and 36% slowing in myopia progression and axial elongation, respectively, over a 2-year timeframe (Ruiz-Pomeda *et al*., 2018). However, this study lacked masking as controls were wearing spectacles, which in turn may have altered compliance with the wearing time (WT) of control correction.

1.5.4.3 OK

In recent decades, OK has become a popular option for myopia management in children. Not only does this modality enhance unaided vision it also provides control of myopia progression as highlighted in a number of studies (see Table 1.4).

Study	Duration	Details	Cohort	Intervention	*Effect
Cho *et al*., 2005	2 years	Self-selected, prospective	7-12 years	OK (n = 35) SV (n = 35)	0.25 mm (46%)
Walline *et al*., 2009	2 years	Prospective, historical controls	8-11 years	OK (n = 28) SVCL (n = 28)	0.32 mm (56%)
Kakita *et al*., 2011	2 years	Self-selected, retrospective	10-15 years	OK (n = 45) SV (n = 60)	0.22 mm (36%)
Cho and Cheung, 2012	2 years	Randomised, single-masked	6-10 years	OK (n = 37) SV (n = 41)	0.27 mm (43%)
Hiraoka *et al*., 2012	5 years	Self-selected, retrospective	8-11 years	OK (n = 29) SV (n = 30)	0.42 mm (30%)
Santodomingo-Rubido *et al*., 2012	2 years	Self-selected, prospective	6-12 years	OK (n = 31) SV (n = 30)	0.22 mm (32%)
Charm and Cho, 2013	2 years	Randomised, single-masked	8-11 years	OK (n = 12) SV (n = 16)	0.32 mm (63%)
Chen *et al*., 2013	2 years	Self-selected, prospective	6-12 years	OK (n = 35) SV (n = 23)	0.33 mm (52%)

Table 1.4 Summary of myopia control studies using OK comparing: SV CL; SV spectacle lens. Adapted from Tang *et al*., 2020. *Mean AL difference between intervention and control participants over study period.

Modern OK designs comprise a central optic zone, a reverse curve zone, an alignment zone and a peripheral zone (Swarbrick, 2006; Lipson *et al*., 2018). The central zone is used to correct the refractive error and also assists with flattening of the central cornea. The steeply designed reverse curve helps to steer corneal reshaping and maximise reduction of myopia, while the alignment zone maintains lens centration. The peripheral zone is important as it allows tear exchange to take place.

It is thought that the myopia control effect facilitated by OK is due to the imposition of myopic defocus on the peripheral retina (Tahhan *et al*., 2003). Following OK treatment, the corneal shape becomes more oblate which leads to a reduction in RPHD (Kang and Swarbrick, 2011). The clinical studies summarised in Table 1.4 demonstrate that the effect of OK on slowing axial elongation ranges from 32% to 63%.

Although the maximum power of myopia reduction possible with OK is yet to be established definitively, -4.00 D is typically taken as the exclusion criteria in most studies (Tang *et al*., 2020). Nevertheless, partial correction of high myopia with OK, with residual refractive error correction with spectacles, still affords a comparable myopia control effect to studies in low to moderate myopes (Charm and Cho, 2013; Wolffsohn *et al*., 2021). While OK is a useful option for myopia control, with significant impact upon mean rates of axial growth retardation, there does appear to be variability in the individual response to this intervention. AL change over 3 years in children receiving OK treatment showed that while 65% showed axial elongation of 0.5 mm or less, 15% of participants experienced growth of more than 1.00 mm (Lipson *et al*., 2018). It has been proposed that age, baseline myopia, corneal profile and pupil size are all possible factors that could influence treatment outcomes (Cho *et al*., 2005; Cho and Cheung, 2012; Hiraoka *et al*., 2012; Santodomingo-Rubido *et al*., 2013; Lipson *et al*., 2018).

1.5.5 Summary

The research to date has shown that careful selection of the method for correction of myopia can, to some extent, dictate the refractive outcome and extent of axial elongation. Undercorrection of myopia should be avoided and a blanket approach to spectacle correction with BFs, MFs or PALs is likely to deliver underwhelming results. However, the encouraging results from the recent DIMS study points towards a more optimistic future for myopia control in spectacle form. In addition, existing soft CLs along with OK have proven to be important options for myopia management in contemporary clinical practice.

1.6 Thesis aims

The literature has highlighted the deleterious effects that hyperopia can have upon visual development and educational attainment throughout childhood, alongside elevating the risk of numerous ocular comorbidities later in life. Research from animal work demonstrates that growth of the eye can be modulated in response to defocus in a range of species. The outcomes from this body work have been successfully translated from the laboratory to the clinic, with a growing armamentarium of interventions available for use in mainstream practice to slow the progression of axial growth in myopes.

Research in the field of refractive error modulation in hyperopia is conspicuous by its absence. With this in mind, the experimental chapters that follow will focus on the potential to accelerate axial growth in children with iso- and anisohyperopia. The aim is to apply the overarching principles highlighted in the animal literature, along with lessons learned from myopia in a human cohort, to assess the impact of imposing hyperopic defocus, on axial growth and refractive error in children with hyperopia.

If the hypothesis is proven, then this body of work offers the potential to mitigate for the effects of hyperopia, thereby permitting normal visual development in childhood and reducing the risk of ocular comorbidity associated with this condition in later life.

2.0 Instrumentation

2.1 Introduction

This chapter outlines details of the equipment utilised throughout the experimental chapters. All measurements were undertaken using equipment available for standard optometric practice following standard operating procedures and professional guidance (The College of Optometrists, Guidance for Professional Practice).

2.2 Assessment of unaided vision and VA

In keeping with other refractive modulation studies (Anstice and Phillips, 2011; Chamberlain *et al*., 2019; Lam *et al*., 2019, Ruiz-Pomeda *et al*., 2019), measures of distance monocular vision, distance monocular VA and near monocular VA were undertaken using logMAR charts to assess the impact of the intervention on these parameters. The standard room illumination was measured at 440 lux using a digital light meter (LX1330B, Dr.meter, US), which falls within the suggested range to avoid the reduction in acuity measures that can arise due to inadequate illumination (Tidbury *et al*., 2016).

The Bailey-Lovie logMAR chart was originally designed to improve the measurement of VA for patients with age-related macular degeneration (AMD) by providing five letters on each line, thereby avoiding problems with letter memorisation (Bailey *et al*., 1976). The chart has uniform spacing between letters which is equivalent to one letter width. Spacing between lines is equal to the letter height of the row below.

Use of logMAR notation mitigates for some of the widely acknowledged issues with Snellen charts (McGraw *et al*., 1995), for example, disproportionate letter crowding between the lower and upper ends of the acuity scale. Other limitations of Snellen charts are the variation in letter legibility and a non-logarithmic scaling of letter size between successive lines; this results in relatively small gaps between lines at the higher end of the acuity scale.

In all experimental chapters, visions and VAs for distance were determined using a computerised test chart (Thomson Software Solutions, Herts, UK) at 6 m equivalent, which allowed changing of optotypes to avoid letter memorisation. For monocular near visual acuity (NVA), a handheld LogMAR chart at 0.25 m was used.

2.3 Assessment of intraocular pressure

Measures of intraocular pressure (IOP) were taken prior to instillation of a cycloplegic using a rebound tonometer, the iCare TA01i (iCare Finland Oy, Helsinki, Finland). The literature has shown that this instrument is adequate as a screening tool in comparison to Goldmann applanation tonometry (GAT) (Clement Clarke International, Harlow, UK) and other handheld tonometers (Fernandes *et al*., 2005; Beasley *et al*., 2013) and is a recommended safeguard when instilling a cycloplegic (The College of Optometrists, Guidance for Professional Practice).

The iCare TA01i rebound tonometer consists of a solenoid and housing, a magnetised probe, and other electronic components. The probe is 40 mm long, 0.3 mm in diameter with a 1.7mm diameter plastic end-tip (Davies *et al*., 2006). The device uses a solenoid to fire the magnetised probe towards the cornea. Electronics monitor the movement of the probe, allowing its speed and direction to be monitored and converted to a measure of IOP. The device is well tolerated, particularly in a paediatric population, and does not require topical anaesthesia (Kageyama *et al*., 2011).

2.4 Cycloplegia

Cycloplegic refraction was undertaken at specified data collection points as outlined in the experimental chapters. 1 drop of cyclopentolate hydrochloride (HCl) 1% in minim form (Bausch + Lomb, Kingston upon Thames, UK) was instilled in each eye to help control accommodation, thereby facilitating more stable measures of objective refraction, which were taken 30 minutes after the drugs were instilled.

Cyclopentolate prevents the action of acetylcholine at muscarinic sites. As muscarinic receptors are abundant in the iris and ciliary body, mydriasis and accommodative inhibition occur with the use of this drug (Kyei *et al*., 2017).

Cyclopentolate is widely used in routine optometric practice as the cycloplegic agent of choice in children due to a relatively short duration of action (Doherty *et al.*, 2019). Importantly, cyclopentolate has been shown to be as effective at achieving adequate cycloplegia but with fewer side effects than other drugs such as atropine (Farhood, 2012). Tropicamide has the benefit of a short duration of action but may not provide sufficient paralysis of accommodation required for accurate refraction in young children, particularly in those with high hyperopia (Yazdani *et al*., 2018). Further, cyclopentolate 1% is recommended as the agent of choice for cycloplegic refraction in children under 12 years of age with 0.5% reserved for those under the age of 6 months (The Royal College of Ophthalmologists, 2012).

2.5 Biometry

Following the approach of earlier work, throughout the experimental chapters, biometric assessment included measures of AL, ACD and CC Walline *et al*., 2013; Aller *et al*., 2016; Ruiz-Pomeda *et al*., 2019). Data were collected using the Zeiss IOLMaster 500 (Zeiss, Oberkochen, Germany) (see Figure 2.1).

Figure 2.1 The IOLMaster 500

The IOLMaster 500 is an instrument that uses the principle of PCI and is considered ideal for the purposes of AL monitoring in clinical practice where available (Gifford *et al*., 2019). It permits a range of ocular parameters to be measured using a non-contact technique, which avoids the need for topical anaesthesia. The instrument works by producing a dual beam of infrared light using a beam splitter and two mirrors, one fixed and the other moveable (see Figure 2.2). As the light enters the eye, it rebounds off the retinal pigment epithelium (RPE) and the anterior surface of the cornea resulting in four emerging beams. A photodetector analyses the interference patterns of the beams which the instrument uses to calculate the AL (Santodomingo-Rubido *et al*., 2002).

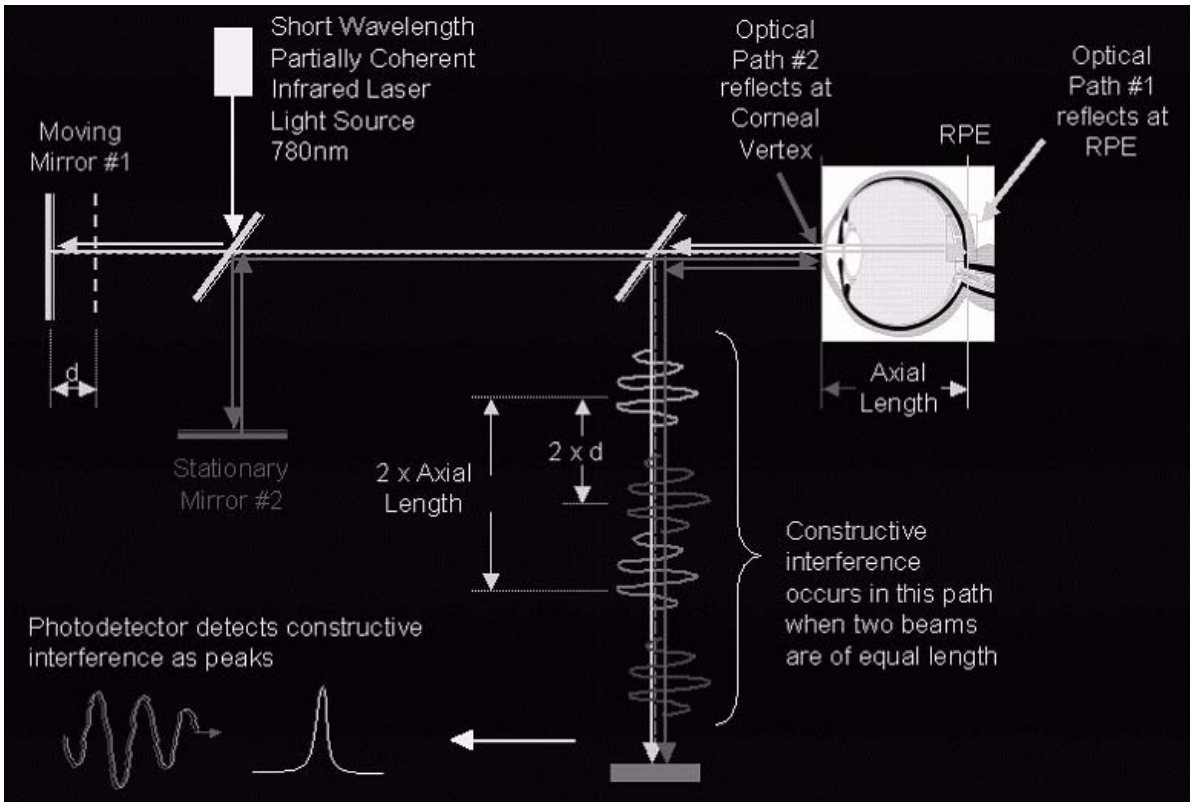

Figure 2.2 The PCI principle utilised by the IOLMaster 500

The IOLMaster 500 is considered to be the gold-standard instrument for taking accurate and reliable biometric measures in both adults (Lam *et al*., 2001; Kielhorn *et al*., 2003) and children (Carkeet *et al*., 2004; Hussin *et al*., 2006; Kimura *et al*., 2007). The PCI method of measurement is reported to give greater repeatability and delivers higher resolution measures than using more traditional contact methods of determining AL, namely A-scans (Santodomingo-Rubido *et al*., 2002; Carkeet *et al*., 2004; Hussin *et al*., 2006). There is conjecture relating to agreement between PCI and A-scan methods with some reporting that the IOLMaster records consistently higher readings for AL than the latter technique (Goyal *et al*., 2003; Rose and Moshegov, 2003) whereas others have found that the two instrument types produce comparable results (Santodomingo-Rubido *et al*., 2002; Hussin *et al*., 2006). As the non-contact method of PCI records the signal from the RPE whereas A-scans require a degree of applanation with the signal originating from the internal limiting membrane (ILM), this may explain the measurement differences reported by some. More recent methods of measuring

AL, for instance, the swept-source technology embedded within the IOLMaster 700, shows good agreement with the PCI method utilised by the IOLMaster 500 (Kunert *et al*., 2016).

Measures of CC are determined by analysing images taken from the anterior surface of the cornea (Elbaz *et al*., 2007); these measures compare well with those taken by other methods including Javal-Schiotz keratometers and videokeratoscopy (Santodomingo-Rubido *et al.*, 2002; Németh *et al.*, 2003).

Measurement of ACD using the IOLMaster 500 is achieved by projecting a narrow optic section, temporal to fixation through the anterior chamber. When the instrument is suitably aligned, the operator presses the joystick button to take a photograph. The distance from the anterior corneal surface and anterior crystalline lens surface is then calculated. When comparing measures taken with different methods, evidence appears equivocal with some reporting shorter ACD when measured by the IOLMaster 500 compared to A-scans (Santodomingo-Rubido *et al.*, 2002) whereas others have demonstrated the opposite (Lam *et al*., 2001).

Calibration of the instrument should be checked prior to each measurement session as outlined in the manufacturer's instructions (Carl Zeiss Meditec). To prepare for measurement, the patient is asked to fixate on the central fixation light while the practitioner evaluates the integrity of the tear film. The practitioner can instruct the patient to blink if the image quality of the mires is poor. Using the overview mode, the practitioner should align the 6 illumination LEDs around the pupil. A traffic light display helps to identify when the optimum measurement position has been achieved, as the light changes from red to yellow and finally, green.

2.5.1 AL and CC measurement

After performing the initial set up using the overview mode described above, the dual measurement mode is selected to capture AL and CC parameters in a single step. Three

measures of CC are taken and displayed as a mean value. Five measures of AL are taken automatically and reported as a composite AL value with the signal-to-noise-ratio (SNR) displayed alongside. For the purposes of experimental data collection, 10 measures of AL were taken for each eye. If a measurement point is not correctly identified, a blue flashing dot appears indicating that a further measurement should be taken. If the instrument detects any measurement errors, for example, deviations within the last three measurements, 'Evaluation' appears in the display indicating that it should be repeated until the results are within tolerance.

2.5.2 ACD measurement

After establishing the initial setup using the overview mode, the ACD mode should be selected and the patient advised to look straight into the yellow light. As a white light is introduced from the side, the patient should be reminded to continue looking at the yellow light only. The manufacturer advises that the best results are obtained with dilated pupils and to minimise potential reflections from other light sources. The instrument displays an average of 5 readings. Measures of ACD were undertaken following cycloplegia at timepoints outlined in Chapters 3 and 4.

2.6 Central refraction

Refraction was undertaken prior to instillation of cyclopentolate 1% HCl using standard optometric techniques, namely using retinoscopy and subjective methods to evaluate the latent and manifest status of refractive error.

Objective central refraction was undertaken 30 minutes after instillation of the cycloplegic agent using the Grand Seiko Auto Ref/Keratometer WAM-5500 autorefractor (Shin-Nippon, Rexxam, Japan) (see Figure 2.3). Use of an autorefractor provides more repeatable results than subjective refraction or other objective techniques such as retinoscopy and is, therefore, the favoured method for use in refractive error studies (Bullimore *et al*., 1998; Davies *et al*., 2003; Mallen *et al*., 2015).

The Grand Seiko Auto Ref/Keratometer WAM-5500 autorefractor has an open-field design which permits the use of real-world targets and control over viewing distance, thereby reducing the effects of proximal accommodation. As such, this type of instrument has become a standard method for use in studies of human refractive error (Logan *et al*., 2005; O'Donoghue *et al*., 2015; Chamberlain *et al*., 2019). Use of an LCD display allows easy alignment and monitoring of fixation. A target of infrared light is projected onto the retina and the reflection is utilised by a moveable lens to focus the device. The output is analysed to provide refraction data in sphero-cylindrical form in increments of 0.01 D and axes to 1°. The instrument provides reliable and valid objective refraction data over a wide range of refractive errors (Sheppard *et al*., 2010)

Figure 2.3 Grand Seiko WAM-5500 autorefractor

2.7 Peripheral refraction

Peripheral refraction measures were undertaken during the studies outlined in Chapters 3 and 4 using the Grand Seiko Auto Ref/Keratometer WAM-5500 autorefractor. Open-field autorefractors are frequently used to measure changes in both central and peripheral refraction over time. Measurements with the Grand Seiko Auto Ref/Keratometer WAM-5500

autorefractor show good repeatability although this decreases with eccentricity, particularly at measures extending to 40° (Moore and Berntsen, 2014). Perhaps unsurprisingly, repeatability has been shown to be better under cycloplegic conditions compared to studies where a cycloplegic was not used (Mallen *et al*., 2001; Davies *et al*., 2003).

Throughout the experimental chapters (see Chapters 3 and 4), peripheral refraction was undertaken under cycloplegic conditions at 30° temporally, 30° nasally, 20° superiorly and 20° inferiorly in line with other examples of peripheral refraction work (Mutti *et al*., 2000; Davies and Mallen, 2009; Chen *et al*., 2010). Participants were asked to fixate Maltese crosses which were placed on a wall to achieve the desired eccentricity points for each of the four peripheral measures. An average of three readings was recorded for each location.

2.8 Pupil size

Assessment of pupil size was undertaken as outlined in the experimental chapters (see Chapters 3 and 4), mirroring the approach taken by others (Anstice and Phillips, 2011; Lam *et al*., 2014). The size of the pupil was recorded using data obtained from the Grand Seiko Auto Ref/Keratometer WAM-5500 autorefractor. The instrument automatically detects the iris boundary and superimposes a best-fit circle to determine pupil size (Sheppard *et al*., 2010). Previous work has shown there is a tendency for the instrument to slightly overestimate pupil size except at the smaller end of pupil size range (Sheppard *et al*., 2010).

Pupil size was assessed under photopic and mesopic conditions. Room illumination was established, using a digital light meter (LX1330B, Dr.meter, US) as 440 lux and 11 lux in photopic and mesopic conditions, respectively; these levels are considered suitable to create the intended light levels for each condition (Jones, 2016).

2.9 Accommodative lag

Lag of accommodation occurs when the accommodative effort is lower than that expected for a given stimulus. For instance, in experimental Chapters 3 and 4, a target placed at 0.33 m provides an accommodative stimulus of 3.00 D. However, an individual's response to this stimulus will often fall short resulting in accommodative lag. As the magnitude of accommodative lag appears to be associated with changes to refractive error, namely progression of myopia (Gwiazda et al., 2004), and in line with previous work (Anstice and Phillips, 2011; Lam *et al*., 2019; Ruiz-Pomeda *et al*., 2019), measures were incorporated into the experimental protocols outlined in Chapters 3 and 4.

An average of 3 measures of accommodative lag were taken using the Grand Seiko Auto Ref/Keratometer WAM-5500 autorefractor. The participant was asked to view a target (Maltese cross) at 0.33 m wearing either their spectacle refractive correction in a trial frame or their prescribed CLs as outlined in the respective study protocols. Participants viewed the target binocularly, but measures of accommodative lag were taken in the dominant eye only (Flitcroft and Morley, 1997). Dominance was established using the hole-in-the-card test which involves holding a rectangular card with a small hole in it of ~ 3cm in diameter and held at arm's length. In this method, the participant is instructed to view the investigator's nose through the hole in the card (see Figure 2.4); this allows the investigator to identify the participant's dominant eye.

Figure 2.4 Hole-in-the-card method for establishing dominance

Some object to the use of so-called ‘sighting dominance’ tests as they fail to identify cases of central eye dominance (Portal and Romano, 1988). Nevertheless, in the context of the refractive error modulation experiments it is desirable to establish a binary outcome through a forced-choice method such as the hole-in-the-card test. Furthermore, the hole-in-the-card test is widely used by others (Lopes-Ferreira *et al*., 2013).

2.10 Amplitude of accommodation

Amplitude of accommodation is typically measured in clinical practice using a Royal Air Force (RAF) rule (Burns *et al*., 2020) and is also a technique used in refractive error modulation studies (Anstice and Phillips, 2011; Lam *et al*., 2019). The test should be performed with the patient’s optimal distance correction *in situ* (Sterner *et al*., 2004). There is debate as to whether the test should be performed with the target pushed up towards the patient or away from them. The result tends to be overestimated when the target is ‘pushed-up’ and underestimated when it is ‘pulled-down’ (Rosenfield and Cohen, 1996). Amplitude of accommodation was performed with the mean of 3 push-up and 3 pull-down measures as outlined in experimental Chapters 3 and 4.

2.11 Contrast sensitivity

Contrast sensitivity (CS) is a useful way to assess visual function in refractive error modulation work (Anstice and Phillips, 2011; Lam *et al*., 2019) by providing more of a real-world measure. Whereas VA assesses an individual’s ability to see small objects at high contrast, CS allows an assessment at lower contrasts (Koch, 1989; Elliott and Hurst, 1990). The CS function (CSF) provides a more complete insight into visual status as VA can be unaffected by certain conditions even though peak CS may be reduced (Pelli and Bex, 2013).

CS can be affected for several reasons including pupil miosis, changes to the crystalline lens and reduction in retinal luminance (Pelli and Bex, 2013). Both central and peripheral CS can

be impaired by wearing MF CLs designed to control myopia progression (Kang *et al*., 2017; Przekoracka *et al*., 2020).

Central CS was measured at timepoints specified in experimental Chapters 3 and 4 both with spectacle and CL correction using a computerised version of the Pelli-Robson chart (Thomson Software Solutions, Herts, UK). The Pelli-Robson chart uses triplets of Sloan letters as stimuli, which progressively reduce in contrast. As the initial stimuli are presented at high contrast, they are easily recognisable by the participant. The use of letters as a target provides a multiple forced-choice method which makes it less prone to guessing than other methods. Each triplet of letters carries a score of 0.15 log units and the range of CS measured is between 0.00-2.25 log units. Single letter measurement can be used with each letter scoring 0.05 log units (Elliott *et al*., 1991). Measurement is ceased when the observer identifies 2 or 3 letters within a given triplet incorrectly. When the test is conducted at a distance of 1 M, the letters equate to approximately 1 CPD allowing measures at low spatial frequency (SF).

2.12 Stereoacuity

An assessment of stereoacuity provides insight into how visual function may be affected by the introduction of novel forms of refractive correction (Lam *et al*., 2019; Ruiz-Pomeda *et al*., 2019), using a test of relatively short duration.

The Frisby Near Stereotest (FNS) (Frisby stereotests, UK) is the most commonly used test in clinical practice for measuring stereoacuity, followed by the TNO (Vancleef and Read, 2019). However, the TNO appears to be more sensitive at detecting subtle binocular abnormalities, for instance, in cases of anisometropia, compared to other tests (Ateiza and Davis, 2019; Nabie *et al*., 2019).

Stereoacuity was measured during specified visits with spectacle and CL correction as outlined in experimental Chapters 3 and 4 using the TNO Randot Stereotest (TNO) at a distance of 40

cm (Edition 15, Laméris Ootech BV, Netherlands). The test measures resolution of fine texture and simulates stereoscopic depth by the horizontal displacement of 2 images while the participant wears red/green glasses. The test figures in the screening plates have disparities of 2000″ whereas the quantitative plates allow measurement of stereoacuity from 480″ to 15″ (Charman and Jennings, 1995). Although, no obvious changes have been made to different editions of this test, there is evidence to show that results are not comparable between, for instance, TNO 13 and TNO 15 (van Doorn *et al*., 2014). Nevertheless, for the purposes of the experiments here, a single edition was used consistently throughout the data collection points.

Visual correction with MF lenses, including those designed for myopia control do not appear to significantly affect stereoacuity (Sha *et al*., 2015; Kang and Wildsoet, 2016; Ruiz-Pomeda *et al*., 2018). Nevertheless, measures of stereoacuity with novel forms of visual correction *in situ* offers value in understanding the visual impact of these interventions on participants. Furthermore, it is important to establish if improvements to stereoacuity can be achieved by taking this unique approach to vision correction in iso- and anisohyperopes.

2.13 CLs

CLs were used as the optical intervention outlined in Chapters 3 and 4. Monthly disposable Biofinity multifocal (centre-near design with an add power of +2.00 D) and Biofinity SV CLs were supplied by CooperVision under the following terms:

'The CLs in the study were supplied free of charge by CooperVision. CooperVision did not sponsor the research and does not support or have an opinion regarding any of the content in the study.' A +2.00 D add was selected in line with previous refractive error modulation studies studies (Anstice and Phillips, 2011; Walline *et al*., 2013; Chamberlain *et al*., 2019a) and aimed to strike a balance between ensuring adequate visual performance (Sha et al., 2015) while imposing peripheral defocus at a level sufficient to test the hypothesis (Walline *et al*., 2020).

Biofinity multifocal CLs are manufactured using a silicone hydrogel material (comfilcon A) with a low modulus and high oxygen transmissibility (Dk/t) of 142 and 160 for the MF and SV modalities, respectively. The MF design is available in centre-distance and centre-near designs with add powers in 0.50 D increments from +1.00 D to +2.50 D (CooperVision, UK). Use of silicone hydrogel *versus* hydrogel material reportedly reduces limbal hyperaemia (Maldonado-Codina *et al*., 2004) and mitigates for the risk of hypoxic changes that can arise with low Dk/t CLs (Covey *et al*., 2001). CLs appear to be safe for children to wear with scarce reports of serious complications in Europe and the US (Bullimore, 2017). Adverse events from clinical trials involving children and CLs are not widely reported (Bullimore, 2017). Interestingly, the rate of corneal infiltrative events in young CL wearers is no higher than in adults and in the range of 8 to 11 years, it may be markedly lower (Bullimore, 2017).

Measures of the power profile of Biofinity multifocal centre-distance lenses show that they have a constant power in the central 1.5 mm zone with an annular zone where the power increases almost linearly and finally an outer zone demonstrating a slow, linear increase in power that is almost independent of the add power (Plainis *et al*., 2013). The centre-near design is broadly similar to the centre-distance design (Plainis *et al*., 2013). In the centre-distance design, the change between the distance to near zone power occurs from 1.6 mm to 2.1 mm radius. In the centre-near design, the transition from the near to distance zone power occurs from 1.2 mm to 2.0 mm radius. The measured add amplitude between the 1.6 mm to 2.1 mm zone for a nominal add power of 2.00 D in the centre-distance design has been reported as 1.01 D. However, for the centre-near design, the power between the 1.6 mm to 2.1 mm zone has been shown to be much closer to its nominal add of 2.00 D being measured at 1.83 D (Kim *et al*., 2017).

Previous CL wear was stated as an exclusion criterion for the studies outlined in Chapters 3 and 4; this was due to the recognised variability in peripheral power profiles across different

SV CL designs, which could potentially impact upon peripheral refractive error (Wagner *et al*., 2015).

3.0 Effect of peripheral defocus on axial growth and refractive error in children with isohyperopia

3.1 Introduction

Despite the known visual consequences and pathological implications of hyperopia (see 1.3.2.1), there has been inertia to address the modulation of refractive error in this cohort of individuals. Given the extensive literature, which reveals the ability to both accelerate and retard axial growth in a range of species (see 1.4.3), it seems plausible that these principles could be applied to children with hyperopia.

Peripheral refraction measures differ between myopes and hyperopes as a result of retinal shape (see 1.4.5); myopes typically exhibit RPH whereas hyperopes tend to be relatively myopic in the periphery. As discussed previously (see 1.5.4.2), soft centre-distance BF CLs have been used as a myopia management strategy in children by correcting distance refractive error through the central optic zone, while simultaneously reducing RPHD through the outer optic zone. For hyperopes, using soft centre-near BF CLs to correct distance refractive error through the central optic zone, while simultaneously *imposing* RPHD through the outer optic zone, could provide a stimulus to axial growth (see Figure 3.1). For example, a child with 5.00 D of hyperopia could be fitted with a centre-near CL with a prescription of +3.00 D add +2.00 D; this specification would provide 5.00 D of refractive correction in the central portion, while imposing 2.00 D of relative hyperopia in the periphery.

Hitherto, there has been no attempt to impose RPHD to modulate refractive error and axial growth in human isohyperopes.

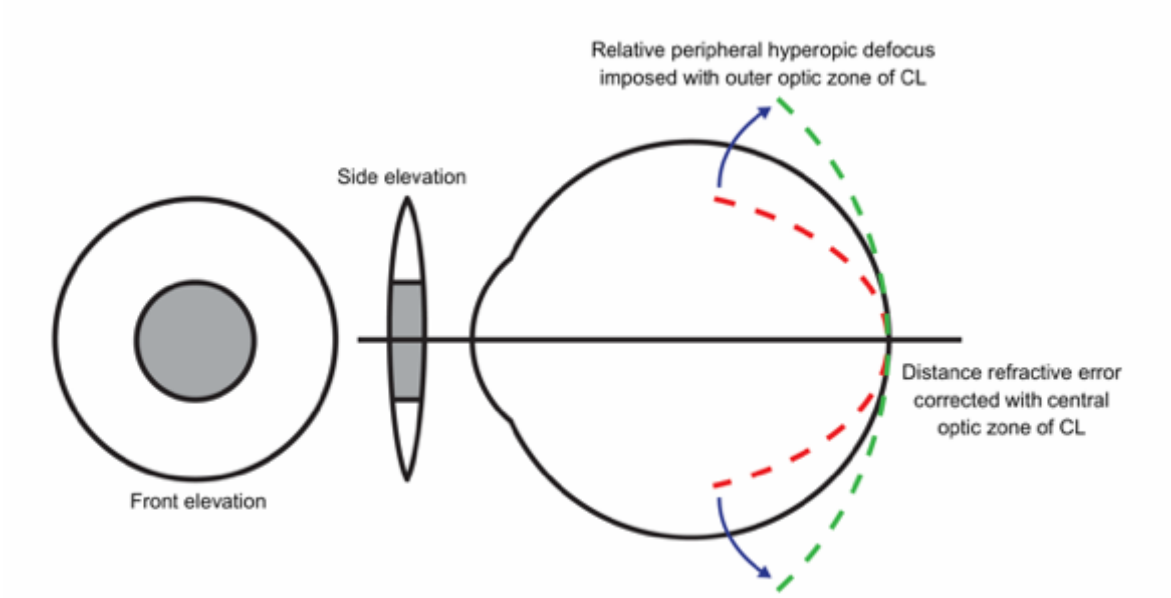

Figure 3.1 Schematic to demonstrate RPHD *imposed* with a centre-near BF CL while full refractive error is corrected centrally

3.2 Objective

The objective of this clinical trial was to understand the natural progression of axial eye growth and refractive error in children with isohyperopia. Considering the paucity of literature to date, this work sought to establish whether axial eye growth and refractive error could be modified in this cohort by imposing relative hyperopic defocus bilaterally using MF CLs.

3.3 Methods

Suitable candidates for the study were recruited by displaying notices at the research venues. Potential participants were also sourced through a database search at the research venues to identify individuals that met the age and refractive error inclusion criteria.

Participants were allocated to 1 of 2 groups:

(1) Natural progression group: refractive error and axial growth was followed over a 3-year period with recruitment open to hyperopes aged between 5 and <20 years-of-age to gain an understanding of natural progression of these parameters in the specified cohort. This arm of

the study did not involve an intervention and therefore served as a control group for the clinical trial.

(2) Hyperopic intervention group: for the intervention arm of the trial, hyperopes wore centre-near MF soft CLs (See Chapter 2.11) between the 6- and 30-month timepoints of the 3-year trial. The CLs provided clear central vision at both distance and near through the near central zone while simultaneously exposing the retina to RPHD from the outer distance zone. Participants aged between 8 and <16 years-of-age were recruited for this arm of the study.

Sample size calculation indicated that 22 participants would be required to achieve 80% power for an effect size of 0.25 at a significance level of 5% using a mixed factor repeated measures ANOVA design (G*Power 3.1, Franz Faul, Universität Kiel, Germany). The aim was to recruit 28 participants to allow for an attrition rate of 20%. Allocation to the respective arms of the study was not randomised. Individuals who were willing and able to use CLs were given the opportunity to be included in the CL arm of the study in the first instance; those who did not want to wear, were unable to handle, or considered unsuitable for CLs, were given the opportunity to participate in the natural progression arm of the study.

Prior to commencing the research, ethical approval was obtained from both the National Health Service Health Research Authority (see Appendix 1) and Aston University's Research Ethics Committees (see Appendix 2) with the study designed to follow the tenets of the Declaration of Helsinki. Each participant, and their parent or guardian where appropriate, was given detailed information regarding the nature of the study, both verbally and in written form; this allowed informed consent and assent to take place prior to participation. The participants were required to complete a short questionnaire to ensure that they met the inclusion criteria (see Appendix 3). The programme of research was registered as a clinical trial: ClinicalTrials.gov NCT02686879. The participant's general practitioner was notified of their inclusion in the study (see Appendix 4).

Inclusion criteria were as follows:

- Aged between 5 and < 20 years-of-age at the initial examination for the natural progression group
- Aged between 8 and < 16 years-of-age at the initial examination for the intervention group
- For participants < 16 years-of-age, parents must have read, understood and signed the informed consent form (see Appendix 5)
- Participants must have read, understood and signed the consent or assent form as appropriate (see Appendix 6 and 7)
- Participants in the intervention group agreed to wear the prescribed CLs for a minimum of 10 hours per day, at least 6 days per week for the 2-year duration of the intervention period
- Be in good general health with no contraindications to CL wear
- Maximum manifest spherical refractive error of +6.00 D
- Maximum manifest cylindrical refractive error of -1.00 D
- Maximum manifest anisometropia of 1.00 D (mean spherical error)
- Minimum mean post-cycloplegic spherical refractive error of +2.00D in the more hyperopic eye for inclusion in the intervention group
- Be competent at handling CLs and understand the instructions given to ensure safe wear.

Exclusion criteria were as follows:

- Previous CL wear
- Participating in another clinical study
- Regular use of medication to treat ocular conditions
- Current use of systemic medication that could impact upon successful CL wear or affect focusing ability
- Known ocular or systemic disease
- Findings identified during CL assessment that would preclude CL wear

- Participants who were not able to provide informed consent without the aid of an interpreter due to lack of funding available for the provision of this facility.

A summary of the procedures conducted at each visit are detailed below and in Table 3.1 and Table 3.2, for the intervention and control groups, respectively. Visits 1 to 7 were undertaken at 6-monthly intervals (± 2 weeks) for all participants. For participants in the intervention group, CL fitting, CL aftercare at 1 to 2 weeks after the initial fitting and CL aftercare 1 month after the first aftercare were also scheduled. At visit 1, all participants completed a background questionnaire (see Appendix 3) to elicit detail of previous ocular history and general health status. At visits 2 to 8, all participants completed a follow-up questionnaire (see Appendix 8) to elicit detail of any changes to ocular history and general health status.

Procedure	Visit 1	Visit 2a	Visit 2b	Visit 2c	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Unaided DV	✅	✅			✅	✅	✅	✅	✅
Subjective refraction	✅	✅			✅	✅	✅	✅	✅
DVA	✅	✅			✅	✅	✅	✅	✅
NVA	✅	✅			✅	✅	✅	✅	✅
Lag of accommodation	✅	✅			✅	✅	✅	✅	✅
Lag with CL *in situ*					✅		✅		
Amplitude of accommodation	✅	✅			✅	✅	✅	✅	✅
Stereoacuity	✅	✅			✅	✅	✅	✅	✅
Stereoacuity with CL in situ					✅		✅		
Cover test	✅	✅			✅	✅	✅	✅	✅
CC	✅	✅			✅	✅	✅	✅	✅
Slit lamp examination	✅	✅				✅		✅	✅
AL	✅	✅			✅	✅	✅	✅	✅
IOP	✅	✅				✅		✅	✅
Post-cycloplegic autorefraction	✅	✅				✅		✅	✅

Peripheral refraction	✅	✅				✅		✅	✅
CS		✅						✅	✅
CS with CL *in situ*			✅					✅	
ACD	✅	✅			✅			✅	✅
Pupil size					✅				
CL fitting		✅							
CL aftercare			✅	✅	✅	✅	✅	✅	
Central refraction with CL *in situ*					✅				
Peripheral refraction with CL *in situ*					✅				

Table 3.1 Procedures undertaken for participants in the intervention group at each visit

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Unaided DV	✅	✅	✅	✅	✅	✅	✅
Subjective refraction	✅	✅	✅	✅	✅	✅	✅
DVA	✅	✅	✅	✅	✅	✅	✅
NVA	✅	✅	✅	✅	✅	✅	✅
Lag of accommodation	✅	✅	✅	✅	✅	✅	✅
Amplitude of accommodation	✅	✅	✅	✅	✅	✅	✅
Stereoacuity	✅	✅	✅	✅	✅	✅	✅
Cover test	✅	✅	✅	✅	✅	✅	✅
CC	✅	✅	✅	✅	✅	✅	✅
Slit lamp examination	✅	✅		✅		✅	✅
AL	✅	✅	✅	✅	✅	✅	✅
IOP	✅	✅		✅		✅	✅
Post-cycloplegic autorefraction	✅	✅		✅		✅	✅
Peripheral refraction	✅	✅		✅		✅	✅
CS		✅				✅	✅
ACD	✅	✅		✅		✅	✅

Pupil size			✅				

Table 3.2 Procedures undertaken for participants in the control group at each visit

3.4 Statistical analysis

All data were analysed using the commercially available software, SPSS, *v*. 25, IBM, New York, U.S.A. Data were examined with mixed factor repeated measures analysis of variance (ANOVA) with one within-subject factor (time) and one between-subject factor (intervention or control). Bonferroni correction was applied and a significance level of $\alpha < 0.05$ used throughout (Armstrong *et al*., 2011; Armstrong *et al*., 2002). Where within-subject factors had three categories or more, sphericity was considered with Greenhouse-Geisser results reported where appropriate. For the primary outcome measures, the mean longitudinal change to AL was the same for right and left eyes ($F_{1,10} = 0.678$, $P = 0.429$); this was also the case for post-cycloplegic refractive error ($F_{1,10} = 0.281$, $P = 0.608$). As such data is presented for the right only, which was selected at random (Armstrong, 2013).

3.5 Results

Data were analysed to compare the primary (see 3.5.1) and secondary (see 3.5.2) outcome measures for the intervention group and control group.

28 participants were recruited in total, with 16 in the intervention group and 12 in the control group. Due to attrition, 5 participants in the intervention group and 2 participants in the control group did not complete the study, with 1 participant transferring from the intervention group to the control group at the second visit (see Table 3.3). In total, 22 participants completed the trial with 11 in the intervention group (8 females and 3 males) with an age range at baseline of 8.42-13.5 years (mean 11.13 SD 1.72 years); these data were normally distributed (Kolmogorov-Smirnov, $Z = 0.166$, $P = 0.200$). The control group consisted of 11 participants (9 females and 2 males) with an age range of 8.33-13.92 years (mean 11.42 SD 2.23 years); these data were normally distributed (Kolmogorov-Smirnov, $Z = 0.187$, $P = 0.200$). The groups

were age-matched (unpaired t-test: t = 0.348, df = 20, P = 0.732). The data presented throughout this chapter are for participants that completed the full trial.

Group	**Timepoint** (months)	**Reason for drop out**
Intervention	6	Difficulty with lens handling
Intervention	6	Cosmetic appearance; transferred to control group
Intervention	8	Difficulty with lens handling
Intervention	9	Poor CL compliance
Intervention	10	Parent cited 'external issues'
Control	7	Moved away
Control	12	Lost to follow up

Table 3.3 Summary of attrition in the intervention and control groups

A summary of descriptive data from questionnaires undertaken at each visit is detailed in Table 3.4 and Table 3.5 for the intervention group and control group, respectively.

	Visit 1		**Follow up visits**
Participant	**History**	**Medication**	**Notes**
1	Full time spectacles at 4 years of age	Nil	Spectacles part-time from Visit 5
2	Full time spectacles at 2 years of age	Nil	
3	Spectacles at 6 years of age for concentrated tasks	Nil	
4	Full time spectacles at 15 months of age	Ventolin	
5	Full time spectacles at 2 years of age	Salbutamol	Beclometasone PRN
6	Full time spectacles at 6 years of age	Desmopressin	No medication from Visit 2
7	Full time spectacles at 5 years of age	Nil	
8	Full time spectacles at 3 years of age	Nil	
9	Full time spectacles at 4 years of age	Nil	
10	Full time spectacles at 4 years of age	Nil	
11	Spectacles at 6 years of age for concentrated tasks	Nil	

Table 3.4 Summary of key information from questionnaires for the intervention group

	Visit 1		Follow up visits
Participant	**History**	**Medication**	**Notes**
1	Full time spectacles at 6 years of age	Nil	
2	Spectacles at 9 years of age for concentrated tasks	Salbutamol	No medication from Visit 4
3	Full time spectacles at 6 years of age	Nil	
4	Full time spectacles at 4 years of age	Nil	
5	Spectacles at 7 years of age for concentrated tasks	Nil	
6	Full time spectacles at 8 years of age	Nil	
7	Full time spectacles at 5 years of age	Nil	
8	Full time spectacles at 4 years of age	Nil	
9	Full time spectacles at 4 years of age	Nil	
10	Full time spectacles at 5 years of age	Nil	
11	Full time spectacles at 2 years of age. Occlusion therapy not adhered to	Nil	

Table 3.5 Summary of key information from questionnaires for the control group

3.5.1 Primary outcome measures

3.5.1.1 Axial growth

Main findings:

- AL increased over time ($F_{(6, 120)} = 27.091$, $P < 0.0005$) for the intervention group but not the control group ($F_{(6, 120)} = 4.663$, $P < 0.0005$). Observed power was 0.986
- For the intervention group, AL did not change during the first 6 months prior to CL wear ($P = 1.000$). Axial growth accelerated throughout the 2 years of intervention ($P = < 0.0005$) but did not change once the intervention was withdrawn for the final 6 months of the trial
- For the control group, AL did not change across the 3-year period ($P = 0.466$).

Pairwise comparisons for between-visit analysis (see Figure 3.2 and Table 3.6) showed that for the intervention group, AL did not change from baseline to the 6-month timepoint (P = 1.000). However, when the intervention was introduced, axial growth accelerated between the 6- and 12-month timepoints (P = 0.003), 12- and 18-month timepoints (P = 0.009), 18- and 24-month timepoints (P = 0.005), and 24- and 30-month timepoints (P = 0.027). Once the intervention was withdrawn, AL did not change between the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.2 and Table 3.6) showed that for the control group, AL did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 0.496), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Due to the inclusion of amblyopes in the study, the analysis was repeated with data removed for the two participants in each group that fell into this category. Reanalysis showed that the key outcome did not change, that is to say, AL increased over time ($F_{(6, 96)} = 19.905$, $P < 0.0005$) for the intervention group but not the control group ($F_{(6, 96)} = 2.859$, $P = 0.013$). Observed power was 0.871.

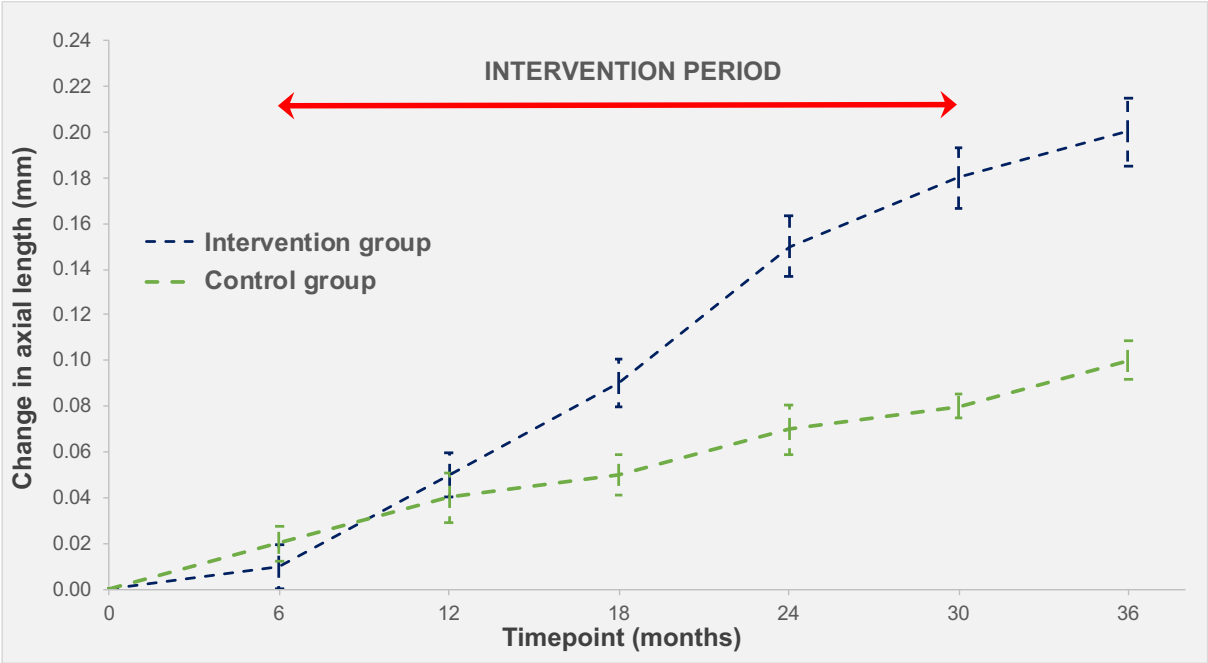

Figure 3.2 Change in AL (mean ± standard error of the mean (SEM))

Timepoint (months)	**AL** (mm)	
Baseline	21.45 ± 0.27	21.81 ± 0.27
6	21.46 ± 0.27	21.83 ± 0.27
12	21.50 ± 0.27	21.85 ± 0.28
18	21.54 ± 0.27	21.86 ± 0.27
24	21.60 ± 0.28	21.88 ± 0.28
30	21.63 ± 0.29	21.89 ± 0.28
36	21.65 ± 0.30	21.91 ± 0.28
	Intervention (n = 11)	**Control** (n = 11)

Table 3.6 AL at each visit (mean ± SEM). Intervention period shaded red

3.5.1.2 Post-cycloplegic refractive error

Main findings:

- Post-cycloplegic MSE refractive error decreased over time ($F_{(4, 80)} = 6.572$, $P < 0.0005$) by a similar amount in both the intervention and control groups ($F_{(4, 80)} = 1.463$, $P = 0.221$)
- Observed power was 0.435 and partial η^2 was 0.068.

Post-cycloplegic MSE refractive error at baseline for the intervention group and the control group were the same (unpaired t-test: t = 1.645, df = 20, P = 0.116).

Pairwise comparisons for between-visit analysis (see Figure 3.3 and Table 3.7) showed that for the intervention group, post-cycloplegic MSE refractive error did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 0.817), 18- and 30-month timepoints (P = 1.000), and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.3 and Table 3.7) showed that for the control group, post-cycloplegic MSE refractive error did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 0.628).

As with AL measures, the data were reanalysed with removal of amblyopic participants. Once again, the outcome remained the same with post-cycloplegic MSE refractive error decreasing over time ($F_{(4, 64)} = 5.260$, $P = 0.001$) by a similar amount in both the intervention and control groups ($F_{(4, 64)} = 1.161$, $P = 0.336$). Observed power was 0.344 and partial η^2 was 0.068.

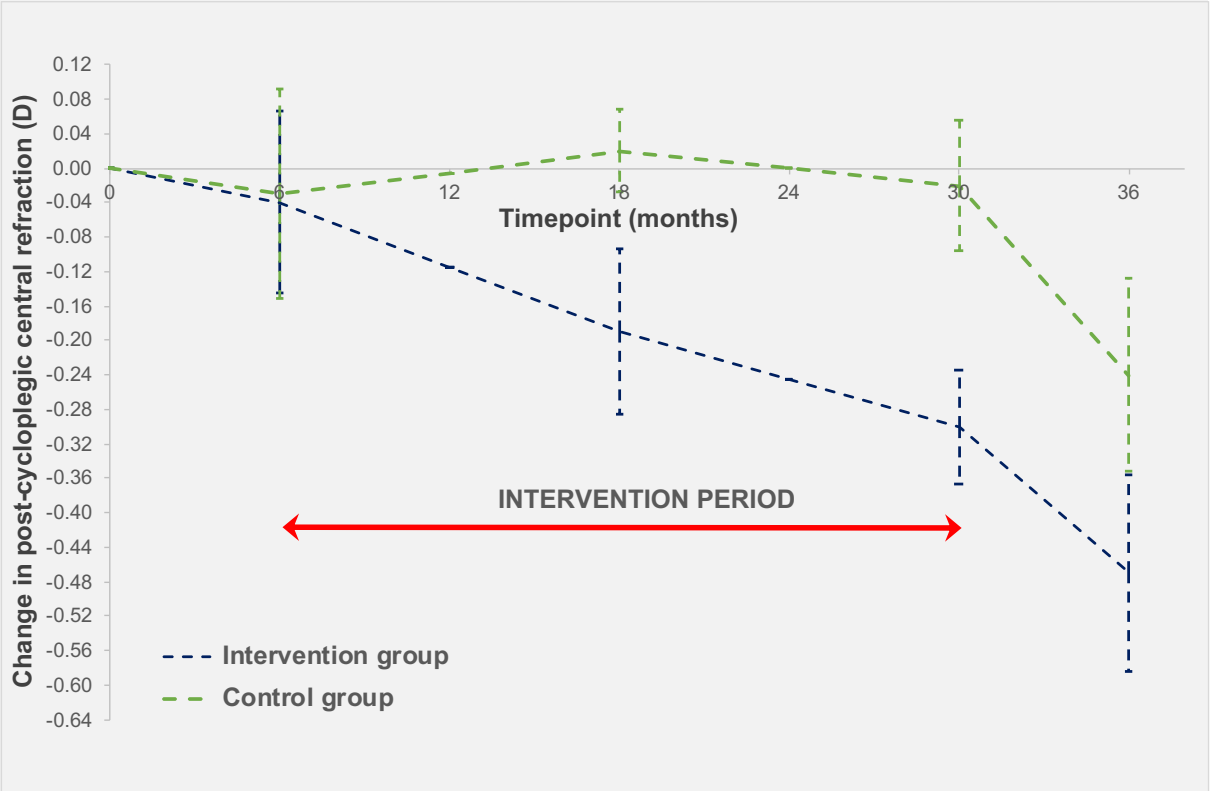

Figure 3.3 Change in MSE post-cycloplegic central refraction (mean ± SEM)

Timepoint (months)	**Refractive error** (D)	
Baseline	+5.23 ± 0.68	+3.78 ± 0.57
6	+5.19 ± 0.67	+3.75 ± 0.56
18	+5.04 ± 0.72	+3.80 ± 0.56
30	+4.93 ± 0.72	+3.76 ± 0.60
36	+4.76 ± 0.69	+3.54 ± 0.59
	Intervention (n = 11)	**Control** (n = 11)

Table 3.7 MSE post-cycloplegic central refractive error at each visit (mean ± SEM). Intervention period shaded red

3.5.2 Secondary outcome measures

3.5.2.1 Unaided DV

Main findings:

- Unaided DV was similar for the intervention and control groups ($F_{(1, 20)} = 2.607$, $P = 0.122$) and did not change over time ($F_{(6, 120)} = 1.099$, $P = 0.367$) in either group ($F_{(6, 120)} = 0.536$, $P = 0.780$).

Pairwise comparisons for between-visit analysis (see Figure 3.4 and Table 3.8) showed that for the intervention group, unaided DV did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 12-month timepoints ($P = 1.000$), 12- and 18-month timepoints ($P = 1.000$), 18- and 24-month timepoints ($P = 1.000$), 24- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 3.4 and Table 3.8) showed that for the control group, unaided DV did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 12-month timepoints ($P = 1.000$), 12- and 18-month timepoints ($P = 1.000$), 18- and 24-month timepoints ($P = 1.000$), 24- and 30-month timepoints ($P = 1.000$), and the 30- and 36-month timepoints ($P = 1.000$).

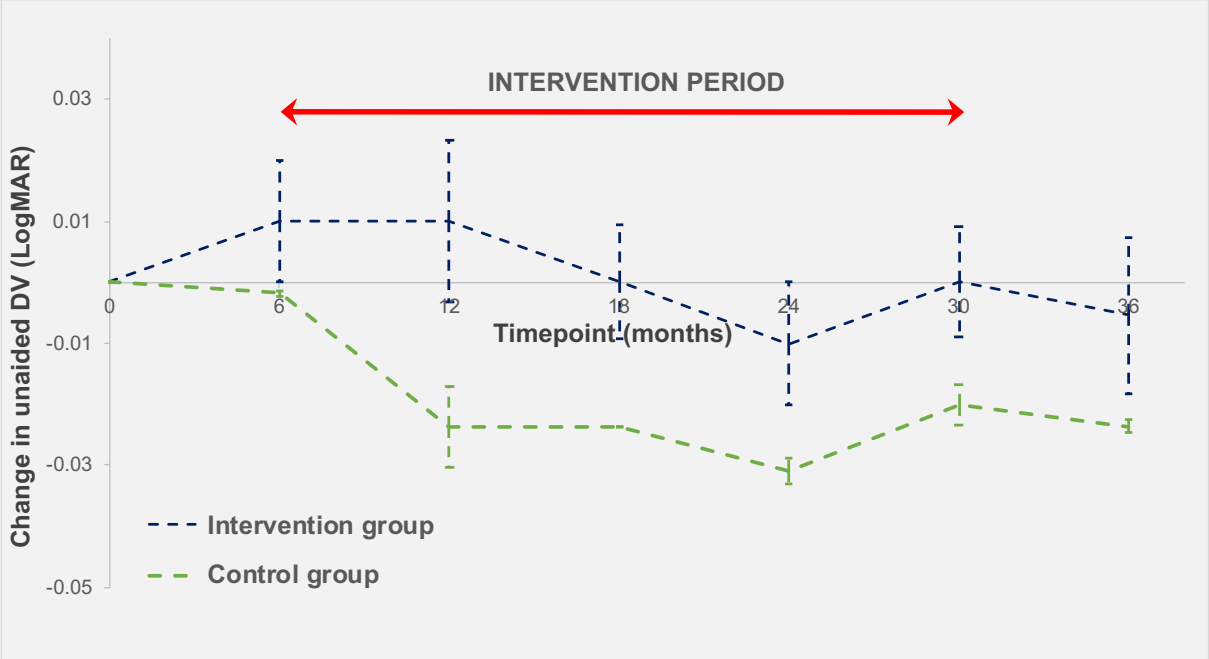

Figure 3.4 Change in unaided DV at 6 m (mean ± SEM)

Timepoint (months)	**DV** (LogMAR)	
Baseline	0.21 ± 0.10	0.06 ± 0.05
6	0.22 ± 0.09	0.06 ± 0.05
12	0.22 ± 0.09	0.04 ± 0.05
18	0.21 ± 0.09	0.04 ± 0.05
24	0.20 ± 0.09	0.03 ± 0.05
30	0.21 ± 0.09	0.04 ± 0.05
36	0.20 ± 0.09	0.04 ± 0.05
	Intervention (n = 11)	**Control** (n = 11)

Table 3.8 Unaided DV at 6 m at each visit (mean ± SEM). Intervention period shaded red

3.5.2.2 Spectacle DVA

Main findings:

- Spectacle DVA was similar for the intervention and control groups ($F_{(1, 20)} = 2.996$, $P = 0.099$) and did not change over time ($F_{(6, 120)} = 0.647$, $P = 0.692$) in either group ($F_{(6, 120)} = 0.713$, $P = 0.640$).

Pairwise comparisons for between-visit analysis (see Figure 3.5 and Table 3.9) showed that for the intervention group, spectacle DVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.5 and Table 3.9) showed that for the control group, spectacle DVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

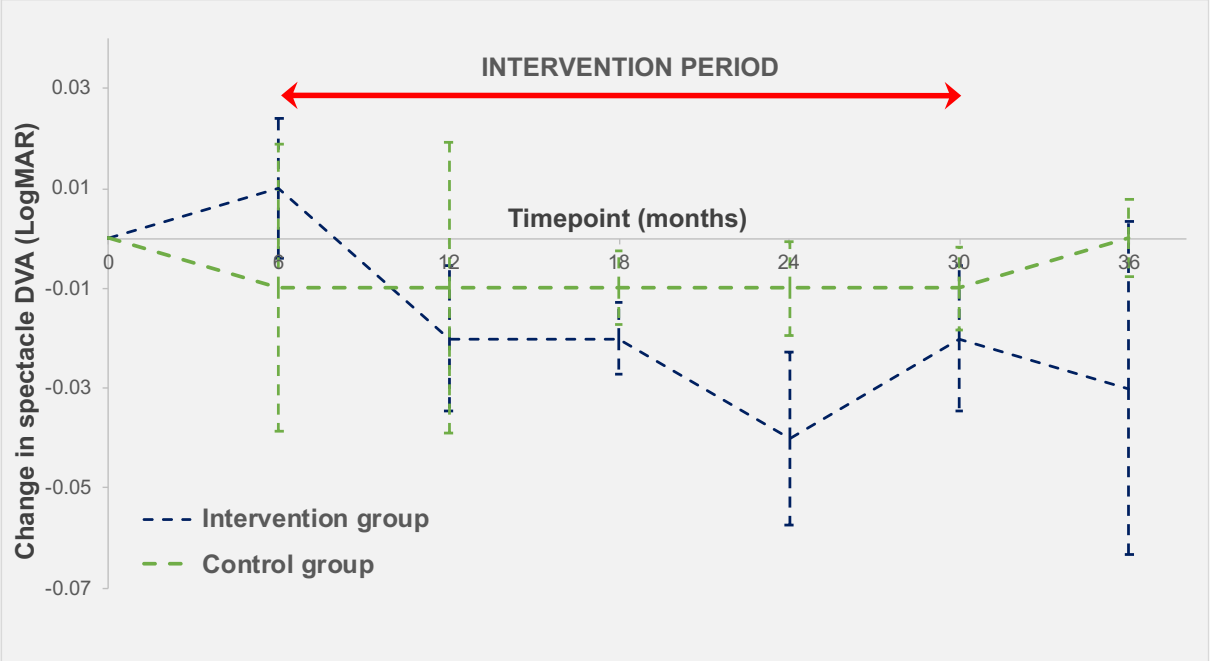

Figure 3.5 Change in spectacle DVA at 6 m (mean ± SEM)

Timepoint (months)	**DVA** (LogMAR)	
Baseline	0.02 ± 0.04	-0.06 ± 0.03
6	0.03 ± 0.04	-0.07 ± 0.02
12	0.00 ± 0.03	-0.07 ± 0.03
18	0.00 ± 0.03	-0.07 ± 0.03
24	-0.02 ± 0.03	-0.07 ± 0.03
30	0.00 ± 0.04	-0.07 ± 0.03
36	-0.01 ± 0.03	-0.06 ± 0.03
	Intervention (n = 11)	**Control** (n = 11)

Table 3.9 Spectacle DVA at 6 m at each visit (mean ± SEM). Intervention period shaded red

3.5.2.3 Spectacle DVA *versus* CL DVA

Main findings:

- DVA was better with spectacles than CLs ($F_{(1, 10)} = 29.321$, $P < 0.0005$) and improved over time ($F_{(4, 40)} = 4.061$, $P = 0.007$) with both forms of correction ($F_{(4, 40)} = 1.315$, $P = 0.281$).

Pairwise comparisons for between-visit analysis (see Figure 3.6 and Table 3.10) showed that with spectacle correction, DVA did not change between the 6- and 12-month timepoints (P = 0.911), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), nor the 24- and 30-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.6 and Table 3.10) showed that with CL correction, DVA did not change between the 6- and 12-month timepoints (P = 0.286), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), nor the 24- and 30-month timepoints (P = 1.000).

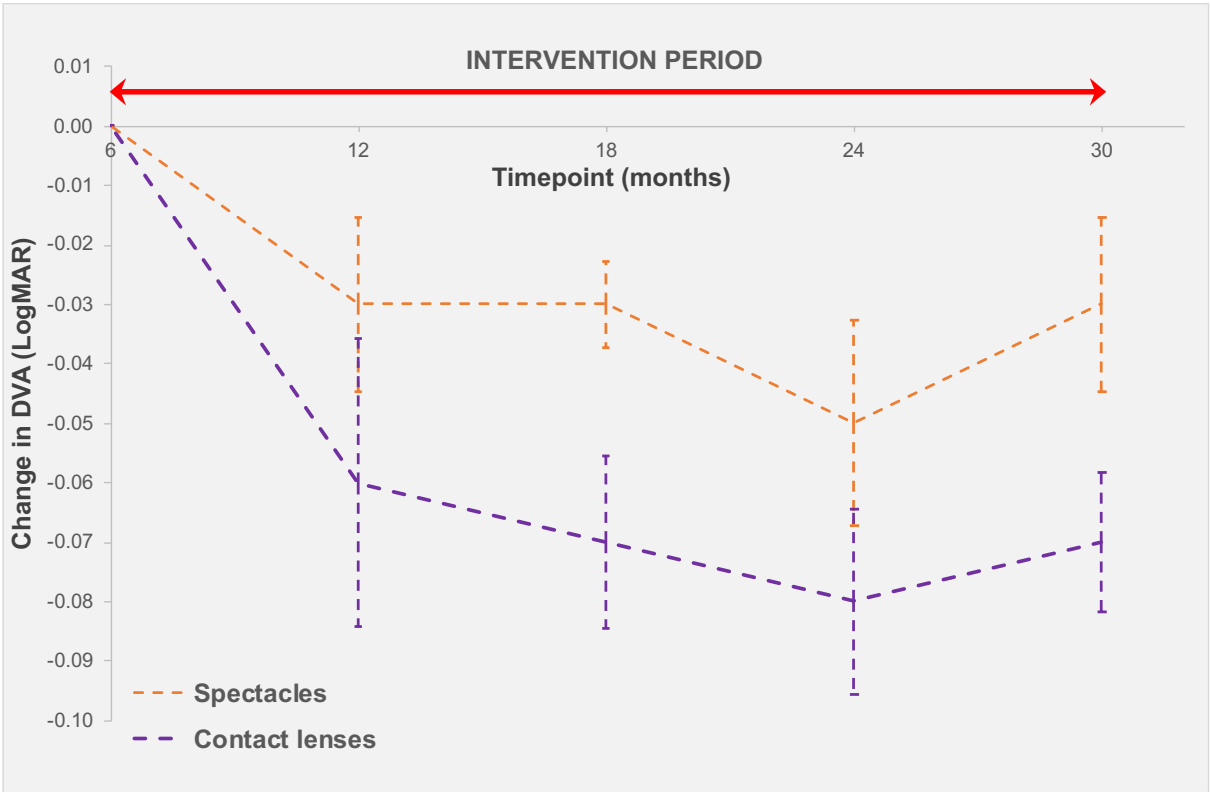

Figure 3.6 Change in spectacle DVA *versus* CL DVA at 6 m throughout the intervention period (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

Timepoint (months)	**DVA** (LogMAR)	
6	0.03 ± 0.04	0.16 ± 0.03
12	0.00 ± 0.03	0.10 ± 0.03
18	0.00 ± 0.03	0.09 ± 0.02
24	-0.02 ± 0.03	0.08 ± 0.03
30	0.00 ± 0.04	0.09 ± 0.03
	Spectacles (n = 11)	**CLs** (n = 11)

Table 3.10 Spectacle DVA *versus* CL DVA at 6 m throughout the intervention period (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

3.5.2.4 Spectacle NVA

Main findings:

- Spectacle NVA was similar for the intervention and control groups ($F_{(1, 20)} = 1.999$, $P = 0.173$) and improved over time ($F_{(6, 120)} = 8.289$, $P < 0.0005$) in both groups ($F_{(6, 120)} = 0.996$, $P = 0.432$).

Pairwise comparisons for between-visit analysis (see Figure 3.7 and Table 3.11) showed that for the intervention group,–spectacle NVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.7 and Table 3.11) showed that for the control group, spectacle NVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000). There was an improvement in mean spectacle NVA between the 12- and 18-month timepoints (P = 0.02) but not between the 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000), nor the 30- and 36-month timepoints (P = 1.000).

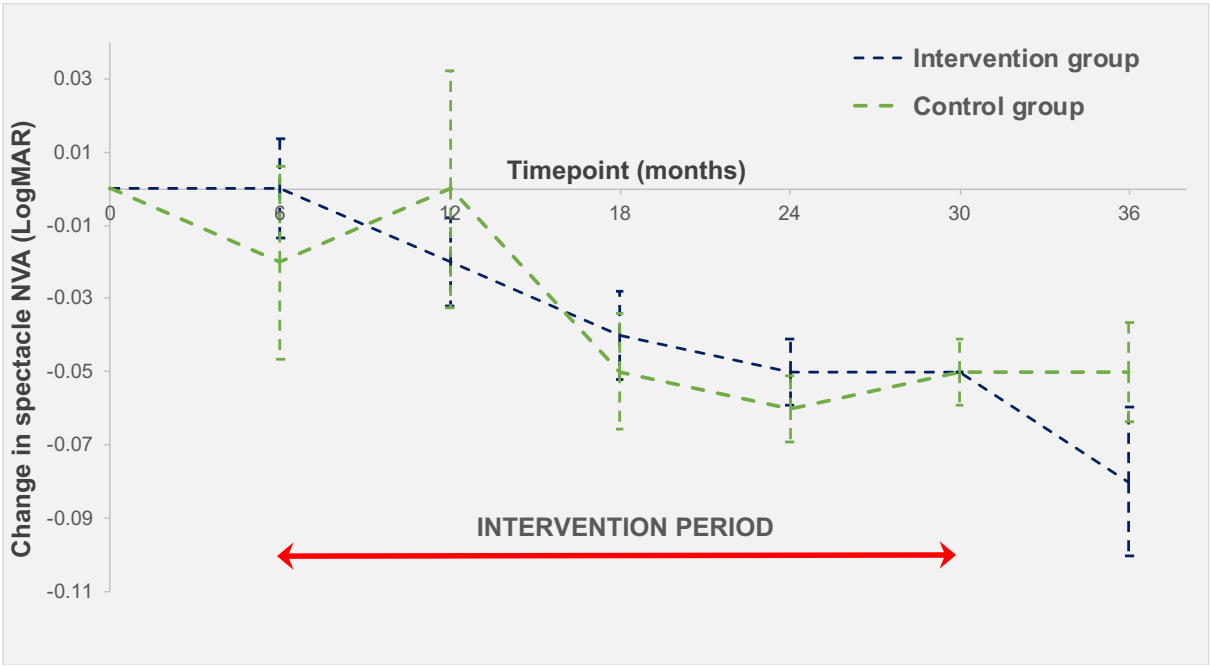

Figure 3.7 Change in spectacle NVA at 0.25 m (mean ± SEM)

Timepoint (months)	**NVA** (LogMAR)	
Baseline	0.23 ± 0.03	0.18 ± 0.03
6	0.23 ± 0.03	0.16 ± 0.02
12	0.21 ± 0.03	0.18 ± 0.04
18	0.19 ± 0.03	0.13 ± 0.03
24	0.18 ± 0.03	0.12 ± 0.03
30	0.18 ± 0.03	0.13 ± 0.03
36	0.15 ± 0.02	0.13 ± 0.02
	Intervention (n = 11)	**Control** (n = 11)

Table 3.11 Spectacle NVA at 0.25 m at each visit (mean ± SEM). Intervention period shaded red

3.5.2.5 Spectacle NVA *versus* CL NVA

Main findings:

- NVA was better with spectacles than CLs ($F_{(1, 10)}$ = 12.000, P = 0.006) and improved over time ($F_{(4, 40)}$ = 5.152, P = 0.002) with both forms of correction ($F_{(4, 40)}$ = 0.154, P = 0.960).

Pairwise comparisons for between-visit analysis (see Figure 3.8 and Table 3.12) showed that with spectacle correction, NVA did not change between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), nor 24- and 30-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.8 and Table 3.12) showed that with CL correction, NVA did not change between the 6- and 12-month timepoints (P = 0.816), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), nor 24- and 30-month timepoints (P = 1.000).

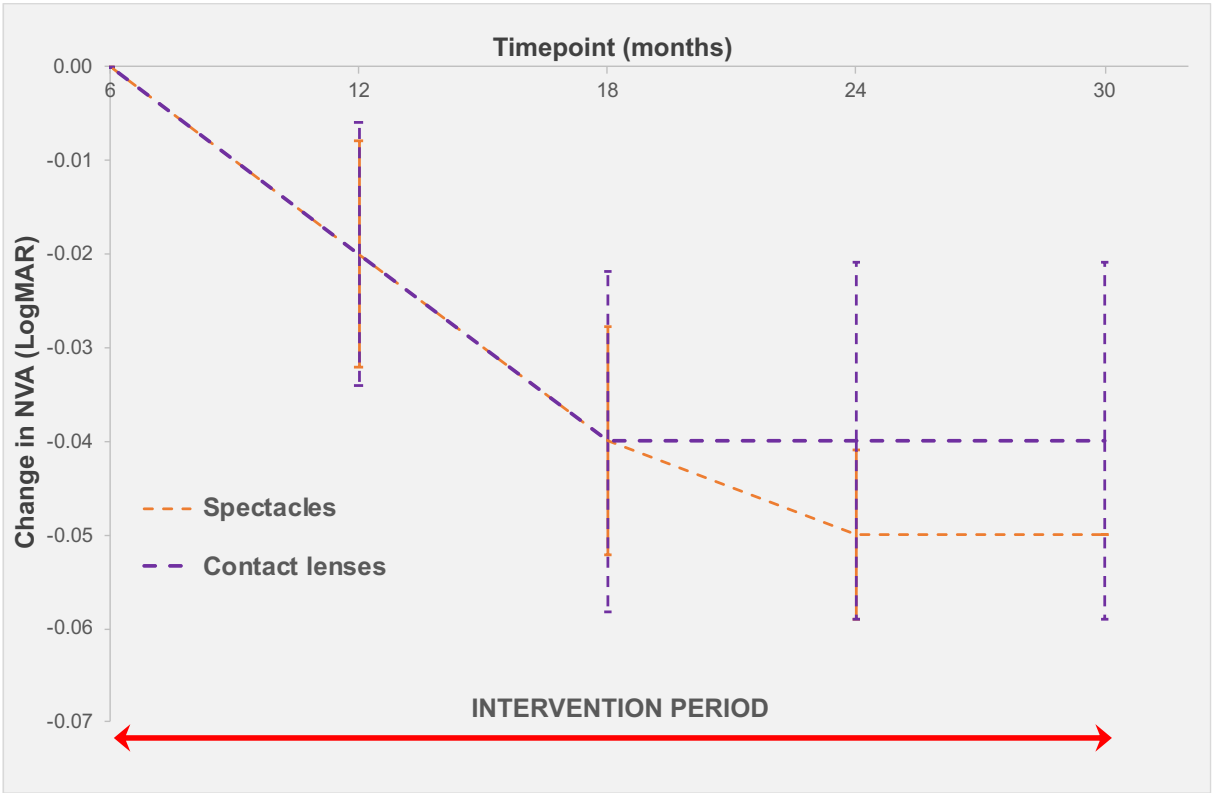

Figure 3.8 Change in spectacle NVA *versus* CL NVA at 0.25 m throughout the intervention period (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

Timepoint (months)	**NVA** (LogMAR)	
6	0.23 ± 0.03	0.26 ± 0.02
12	0.21 ± 0.03	0.24 ± 0.02
18	0.19 ± 0.03	0.22 ± 0.03
24	0.18 ± 0.03	0.22 ± 0.02
30	0.18 ± 0.03	0.22 ± 0.02
	Spectacles (n = 11)	**CLs** (n = 11)

Table 3.12 Spectacle NVA *versus* CL NVA at 0.25 m throughout the intervention period (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

3.5.2.6 Stereoacuity with spectacle correction

Main findings:

- Stereoacuity with spectacles was similar for the intervention and control groups ($F_{(1, 18)}$ = 0.856, P = 0.367) and did not change over time ($F_{(6, 108)}$ = 0.838, P = 0.544) for either group ($F_{(6, 120)}$ = 0.350, P = 0.908).

Pairwise comparisons for between-visit analysis (see Figure 3.9 and Table 3.13) showed that for the intervention group, stereoacuity did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.9 and Table 3.13) showed that for the control group, stereoacuity did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

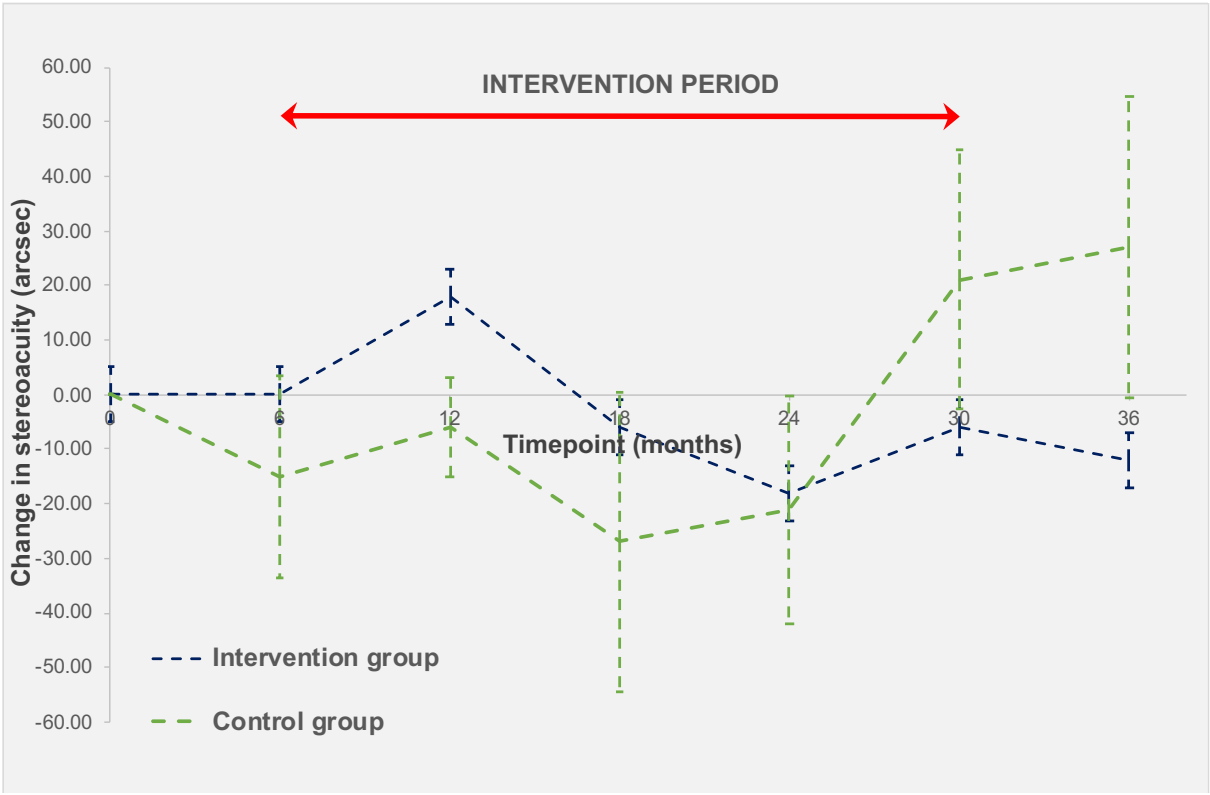

Figure 3.9 Change in stereoacuity with spectacle correction (mean ± SEM). Excludes participants that were unable to complete the grading plates

Timepoint (months)	**Stereoacuity** (arcsec)	
Baseline	144.00 ± 41.18	99.00 ± 42.44
6	132.00 ± 39.80	102.00 ± 42.00
12	150.00 ± 40.25	111.00 ± 41.96
18	126.00 ± 40.45	90.00 ± 18.44
24	113.33 ± 17.61	98.18 ± 22.88
30	133.33 ± 45.28	130.91 ± 40.53
36	126.67 ± 45.93	136.36 ± 53.73
	Intervention (n = 10)	**Control** (n = 10)

Table 3.13 Stereoacuity at each visit (mean ± SEM). Intervention period shaded red. Excludes participants that were unable to complete the grading plates

3.5.2.7 Stereoacuity: spectacle correction *versus* CL correction

Main findings:

- Stereoacuity was better with spectacles than CLs ($F_{(1, 9)} = 7.071$, $P = 0.026$) and did not change over time ($F_{(1, 9)} = 0.000$, $P = 1.000$) with either form of correction ($F_{(1, 9)} = 3.692$, $P = 0.087$).

Pairwise comparisons for between-visit analysis (see Table 3.14) showed that with spectacle correction, stereoacuity was similar at the 12- and 24-month timepoints ($P = 0.373$).

Pairwise comparisons for between-visit analysis (see Table 3.14) showed that with CL correction, stereoacuity did not change between the 12- and 24-month timepoints ($P = 0.168$).

Timepoint (months)	**Stereoacuity** (arcsec)	
12	150.00 ± 40.25	192.00 ± 50.44
24	126.00 ± 20.88	216.00 ± 49.15
	Spectacles (n = 10)	**CLs** (n = 10)

Table 3.14 Stereoacuity with spectacle correction *versus* CL correction (mean ± SEM). Intervention period shaded red. Excludes 1 participant who was unable to complete the grading plates

3.5.2.8 Cover test with spectacle correction

A summary of binocular status with spectacle correction at distance and near for the intervention and control participants is detailed in Table 3.15 and Table 3.16, respectively.

	Cover test	
Participant	**Distance at 6 m**	**Near at 0.25 m**
1	Orthophoria	Orthophoria
2	Orthophoria	Orthophoria
3	Orthophoria	Orthophoria
4	Small esophoria	Small esophoria
5	Orthophoria	Orthophoria
6	Right esotropia	Right esotropia
7	Alternating esotropia	Alternating esotropia
8	Orthophoria	Orthophoria
9	Orthophoria	Orthophoria
10	Orthophoria	Orthophoria
11	Right esotropia	Right esotropia

Table 3.15 Cover test with spectacle correction at distance and near for the intervention group

	Cover test	
Participant	**Distance at 6 m**	**Near at 0.25 m**
1	Orthophoria	Orthophoria
2	Orthophoria	Orthophoria
3	Orthophoria	Orthophoria
4	Orthophoria	Small exophoria
5	Orthophoria	Orthophoria
6	Orthophoria	Orthophoria
7	Orthophoria	Small exophoria
8	Orthophoria	Orthophoria
9	Orthophoria	Small exophoria
10	Orthophoria	Orthophoria
11	Left esotropia	Left esotropia

Table 3.16 Cover test with spectacle correction at distance and near for the control group

3.5.2.9 CS with spectacle correction

Main findings:

- CS with spectacle correction was better in the control group than the intervention group ($F_{(1, 20)} = 5.125$, $P = 0.035$). This measure did not change over time ($F_{(2, 40)} = 1.296$, $P = 0.285$) in either group ($F_{(2, 40)} = 0.432$, $P = 0.652$).

Pairwise comparisons for between-visit analysis (see Figure 3.10 and Table 3.17) showed that for the intervention group, CS with spectacle correction did not change between the 6- and 30-month timepoints (P = 1.000), nor between the 30- and 36-month timepoints (P = 0.716).

Pairwise comparisons for between-visit analysis (see Figure 3.10 and Table 3.17) showed that for the control group, CS with spectacle correction was the same between the 6- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

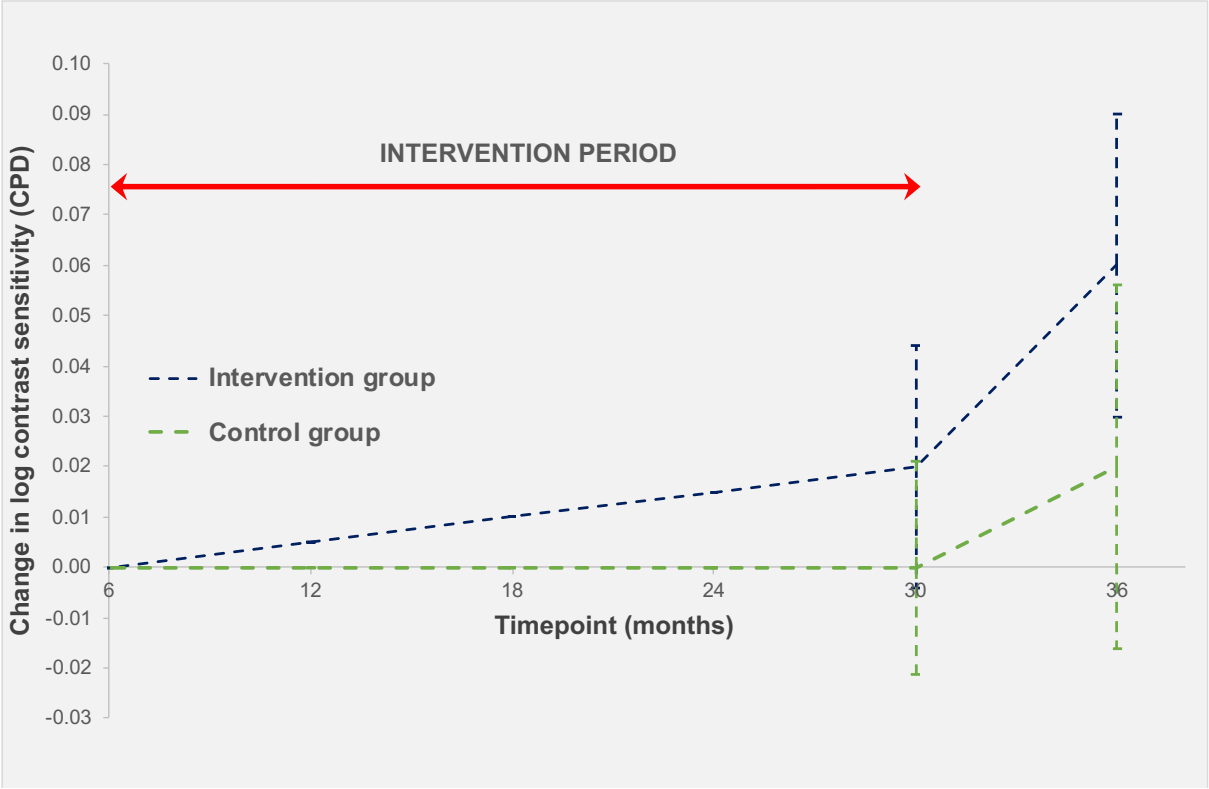

Figure 3.10 Change in CS with spectacle correction at 1 m (mean ± SEM)

Timepoint (months)	**Log CS** (CPD)	
6	1.51 ± 0.04	1.62 ± 0.03
30	1.53 ± 0.03	1.62 ± 0.03
36	1.57 ± 0.02	1.64 ± 0.03
	Intervention (n = 11)	**Control** (n = 11)

Table 3.17 CS with spectacle correction at 1 m. Intervention period shaded red

3.5.2.10 CS: spectacle correction *versus* CL correction

Main findings:

- CS was similar with spectacle correction and CL correction ($F_{(1, 10)} = 0.000$, $P = 1.000$) and did not change over time ($F_{(1, 10)} = 1.379$, $P = 0.267$) with either form of correction ($F_{(1, 10)} = 1.000$, $P = 0.341$).

Pairwise comparisons for between-visit analysis (see Table 3.18) showed that with spectacle correction, CS was similar at the 6- and 30-month timepoints (P = 0.588).

Pairwise comparisons for between-visit analysis (see Table 3.18) showed that with CL correction, CS was similar at the 6- and 30-month timepoints (P = 0.192).

Timepoint (months)	**Log CS** (Cycles per degree) (CPD))	
6	1.51 ± 0.04	1.50 ± 0.03
30	1.53 ± 0.03	1.54 ± 0.03
	Spectacles (n = 11)	**CLs** (n = 11)

Table 3.18 CS with spectacle correction *versus* CL correction at 1 m (mean ± SEM). Intervention period shaded red. Measures at the first timepoint taken at the first CL aftercare visit

3.5.2.11 CC

Main findings:

- CC was similar for the intervention and control participants ($F_{(1, 20)} = 0.578$, $P = 0.456$) and did not change over time ($F_{(6, 120)} = 0.547$, $P = 0.772$) in either group ($F_{(6, 120)} = 0.525$, $P = 0.788$).

Pairwise comparisons for between-visit analysis (see Figure 3.11 and Table 3.19) showed that for the intervention group, CC did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 12-month timepoints ($P = 1.000$), 12- and 18-month timepoints ($P = 1.000$), 18- and 24-month timepoints ($P = 1.000$), 24- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 3.11 and Table 3.19) showed that for the control group, CC did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 12-month timepoints ($P = 1.000$), 12- and 18-month timepoints ($P = 1.000$), 18- and 24-month timepoints ($P = 1.000$), 24- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

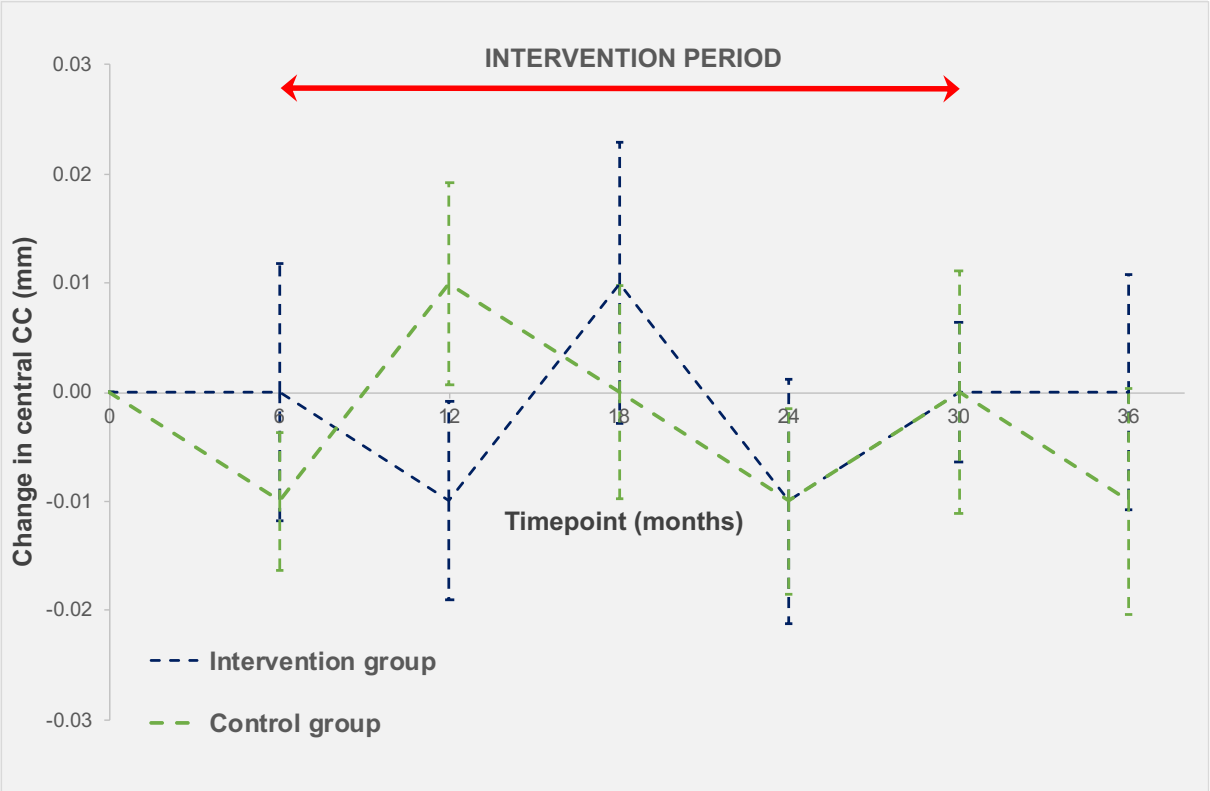

Figure 3.11 Change in CC (mean ± SEM)

Timepoint (months)	**CC** (mm)	
Baseline	7.80 ± 0.08	7.71 ± 0.09
6	7.80 ± 0.08	7.70 ± 0.10
12	7.79 ± 0.08	7.72 ± 0.09
18	7.81 ± 0.08	7.71 ± 0.09
24	7.79 ± 0.08	7.70 ± 0.09
30	7.80 ± 0.08	7.71 ± 0.09
36	7.80 ± 0.08	7.70 ± 0.09
	Intervention (n = 11)	**Control** (n = 11)

Table 3.19 CC at each visit (mean ± SEM). Intervention period shaded red

3.5.2.12 ACD

Main findings:

- ACD was similar for the intervention and control groups ($F_{(1, 20)} = 1.167$, $P = 0.293$). ACD changed over time ($F_{(4, 80)} = 7.041$, $P < 0.0005$) in both the intervention group and the control group ($F_{(4, 80)} = 0.740$, $P = 0.568$).

Pairwise comparisons for between-visit analysis (see Figure 3.12 and Table 3.20) showed that for the intervention group, ACD did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 0.211$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 3.12 and Table 3.20) showed that for the control group, ACD did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 0.386$).

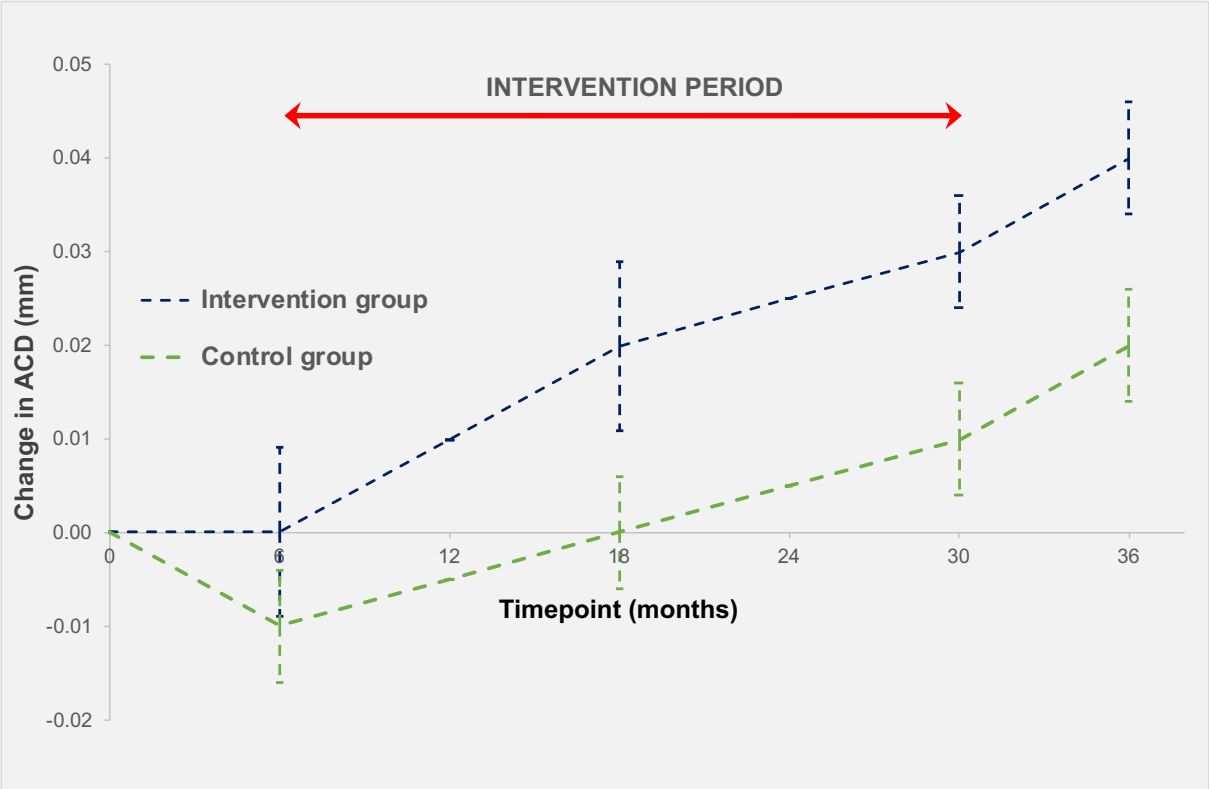

Figure 3.12 Change in ACD (mean ± SEM)

Timepoint (months)	**ACD** (mm)	
Baseline	3.32 ± 0.11	3.48 ± 0.07
6	3.32 ± 0.12	3.47 ± 0.07
18	3.34 ± 0.11	3.48 ± 0.06
30	3.35 ± 0.12	3.49 ± 0.07
36	3.36 ± 0.12	3.50 ± 0.07
	Intervention (n = 11)	**Control** (n = 11)

Table 3.20 ACD at each visit (mean ± SEM). Intervention period shaded red

3.5.2.13 Pupil size

Main findings:

- Pupil size was similar for the intervention and control groups ($F_{(3, 43)} = 2.250$, $P = 0.293$) and was smaller under photopic conditions than mesopic conditions ($F_{(3, 43)} = 12.883$, $P = 0.001$) in both the intervention group and the control group ($F_{(3, 43)} = 0.103$, $P = 0.750$) (see Table 3.21).

	Pupil size (mm)			
Timepoint (months)	Intervention - photopic	Control - photopic	Intervention - mesopic	Control - mesopic
12	5.92 ± 0.21	6.23 ± 0.16	6.58 ± 0.16	6.78 ± 0.15

Table 3.21 Pupil size in photopic and mesopic conditions for the intervention and control participants (mean ± SEM)

3.5.2.14 Amplitude of accommodation

Main findings:

- Amplitude of accommodation was similar for the intervention and control groups ($F_{(1, 20)} = 0.049$, $P = 0.827$) and did not change over time ($F_{(6, 120)} = 1.469$, $P = 0.195$) in either group ($F_{(6, 120)} = 0.275$, $P = 0.948$).

Pairwise comparisons for between-visit analysis (see Figure 3.13 and Table 3.22) showed that for the intervention group, amplitude of accommodation did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.13 and Table 3.22) showed that for the control group, amplitude of accommodation did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

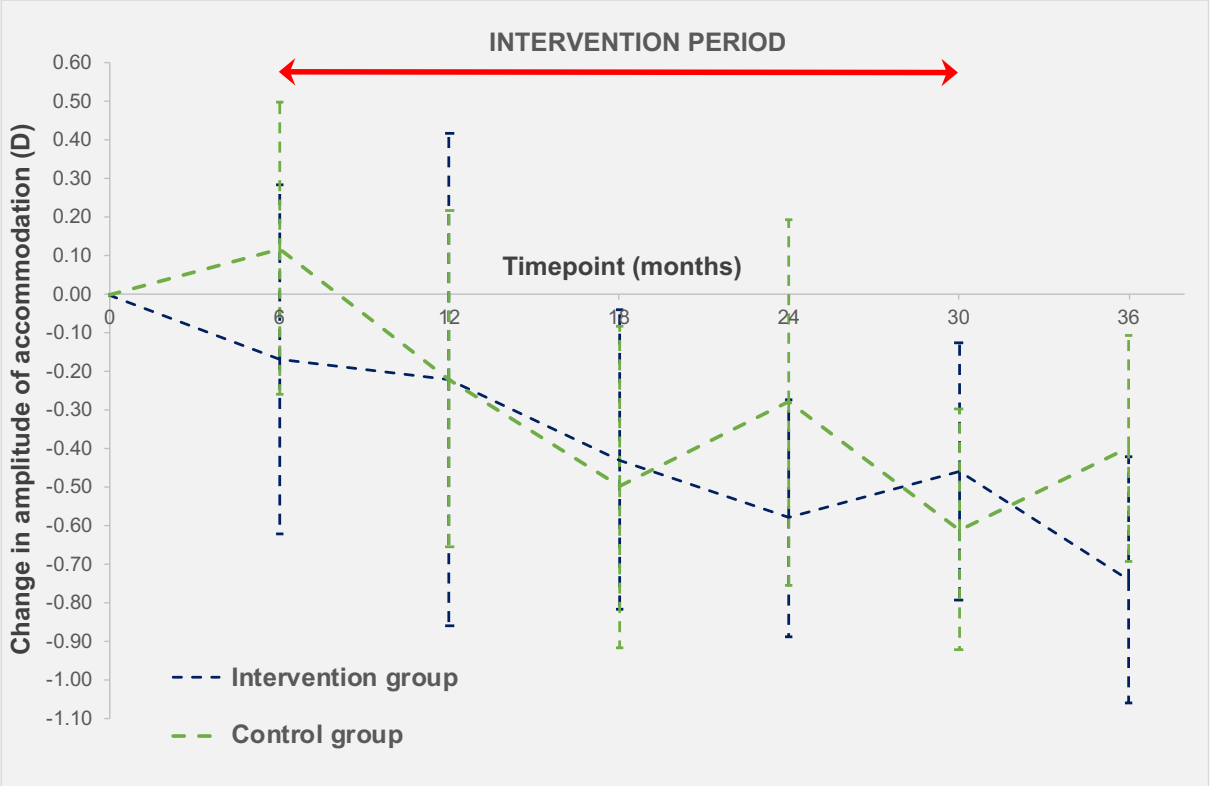

Figure 3.13 Change in amplitude of accommodation (mean ± SEM)

Timepoint (months)	**Amplitude of accommodation** (D)	
Baseline	11.61 ± 0.53	11.61 ± 0.46
6	11.44 ± 0.51	11.73 ± 0.38
12	11.39 ± 0.50	11.39 ± 0.27
18	11.18 ± 0.40	11.11 ± 0.39
24	11.03 ± 0.37	11.33 ± 0.44
30	11.15 ± 0.43	11.00 ± 0.36
36	10.86 ± 0.34	11.21 ± 0.36
	Intervention (n = 11)	**Control** (n = 11)

Table 3.22 Amplitude of accommodation at each visit (mean ± SEM). Intervention period shaded red

3.5.2.15 Lag of accommodation with spectacle correction

Main findings:

- Lag of accommodation with spectacle correction was similar for the intervention and control groups ($F_{(1, 20)} = 2.139$, $P = 0.159$) and increased over time ($F_{(6, 120)} = 3.477$, $P = 0.003$) in both groups ($F_{(6, 120)} = 1.793$, $P = 0.106$).

Pairwise comparisons for between-visit analysis (see Figure 3.14 and Table 3.23) showed that for the intervention group, lag of accommodation with spectacle correction did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.14 and Table 3.23) showed that for the control group, lag of accommodation with spectacle correction did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P

= 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000), and the 30- and 36-month timepoints (P = 1.000).

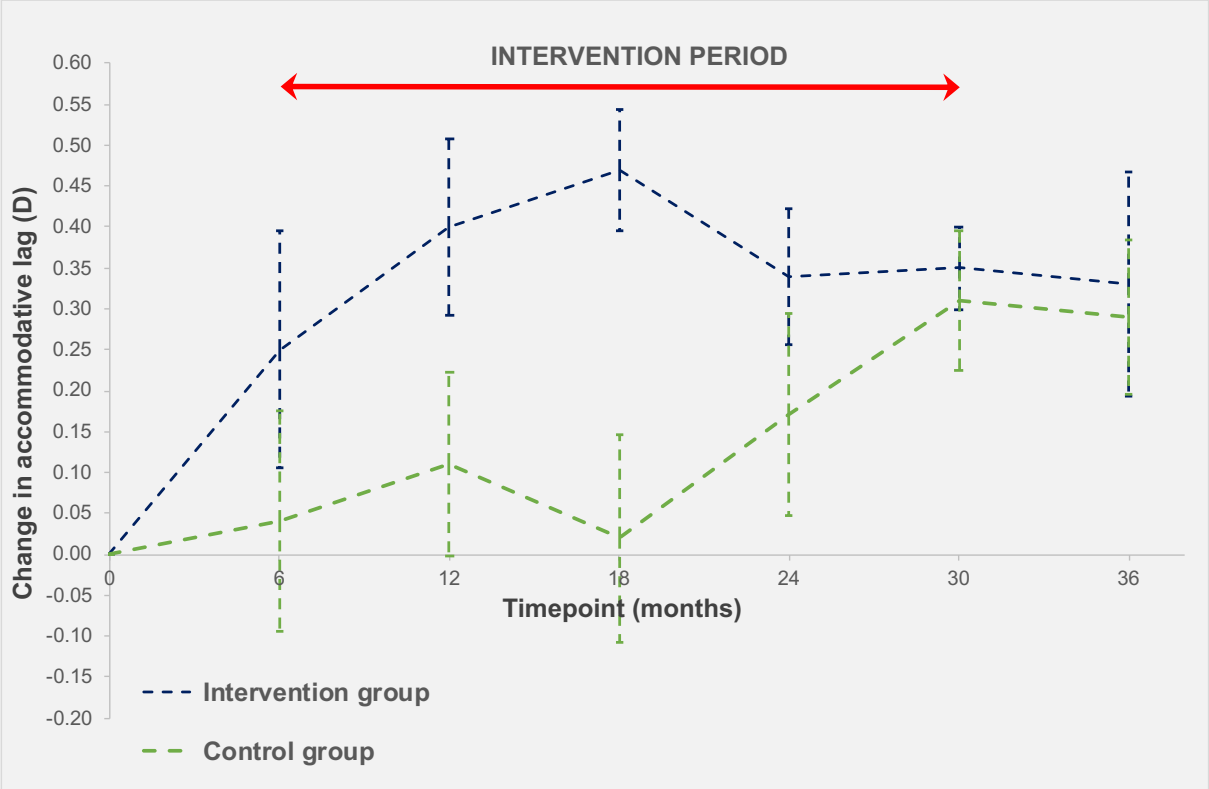

Figure 3.14 Change in accommodative lag with spectacle correction for a target at 0.33 m (mean ± SEM)

Timepoint (months)	**Accommodative lag** (D)	
Baseline	0.76 ± 0.11	0.82 ± 0.12
6	1.01 ± 0.10	0.86 ± 0.14
12	1.16 ± 0.08	0.93 ± 0.09
18	1.23 ± 0.09	0.84 ± 0.10
24	1.10 ± 0.05	0.99 ± 0.10
30	1.11 ± 0.06	1.13 ± 0.09
36	1.09 ± 0.10	1.11 ± 0.08
	Intervention (n = 11)	**Control** (n = 11)

Table 3.23 Accommodative lag with spectacle correction for a target at 0.33 m (mean ± SEM). Intervention period shaded red

3.5.2.16 Lag of accommodation: spectacle correction versus CL correction

Main findings:

- For the intervention group, lag of accommodation was higher with CL correction than spectacle correction ($F_{(1, 10)} = 5.94$, $P = 0.035$) and did not change over time ($F_{(1, 10)} = 0.516$, $P = 0.489$) with either form of correction ($F_{(1, 10)} = 0.101$, $P = 0.757$).

Pairwise comparisons for between-visit analysis (see Table 3.24) showed that with spectacle correction, lag of accommodation was similar at the 12- and 24-month timepoints ($P = 0.476$).

Pairwise comparisons for between-visit analysis (see Table 3.24) showed that with CL correction, lag of accommodation was similar at the 12- and 24-month timepoints ($P = 0.591$).

Timepoint (months)	**Accommodative lag** (D)	
12	1.16 ± 0.08	1.48 ± 0.20
24	1.10 ± 0.05	1.34 ± 0.18
	Spectacles (n = 11)	**CLs** (n = 11)

Table 3.24 Accommodative lag with spectacle correction *versus* CL correction for a target at 0.33 m (mean ± SEM). Intervention period shaded red

3.5.2.17 Central CL power

Main findings:

- Central CL power reduced over time ($F_{(4, 40)} = 21.174$, $P < 0.0005$).

Pairwise comparisons for between-visit analysis (see Figure 3.15 and Table 3.25) showed that central CL power did not change between the 6- and 12-month timepoints ($P = 0.162$), nor between the 12- and 18-month timepoints ($P = 0.379$). There was a decrease in central CL

power between the 18- and 24-month timepoints (P = 0.019) but not between the 24- and 30-month timepoints (P = 1.000).

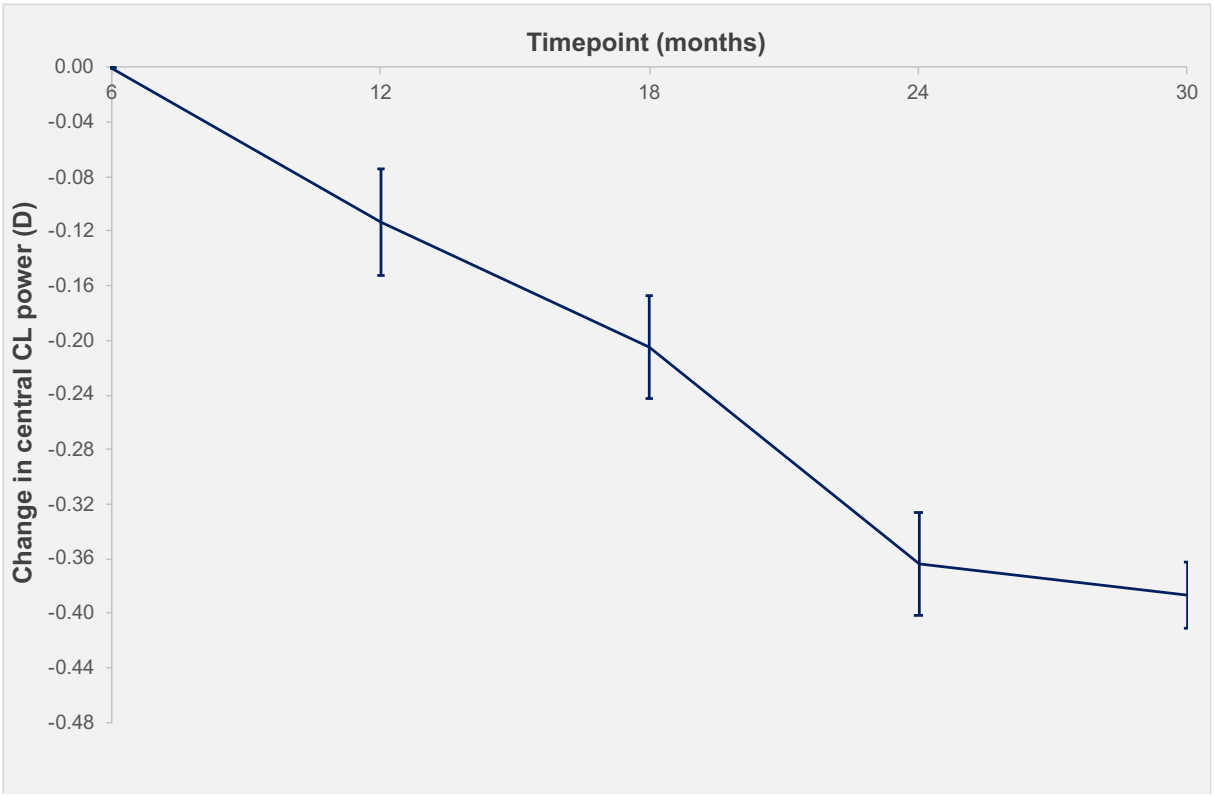

Figure 3.15 Change in central CL power (mean ± SEM)

Timepoint (months)	**Central CL power** (D)
6	3.93 ± 0.74
12	3.82 ± 0.73
18	3.73 ± 0.74
24	3.57 ± 0.73
30	3.55 ± 0.74

Table 3.25 Central CL power (mean ± SEM)

3.5.2.18 CL WT

Main findings:

- CL WT changed over time ($F_{(4, 40)} = 3.652$, P = 0.013) with a significant increase over the first 6 months of wear and remained at that level thereafter.

Pairwise comparisons for between-visit analysis (see Figure 3.16 and Table 3.26) showed that mean weekly CL WT increased between the 6- and 12-month timepoints (P = 0.049), but not between the 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000) nor the 24- and 30-month timepoints (P = 1.000).

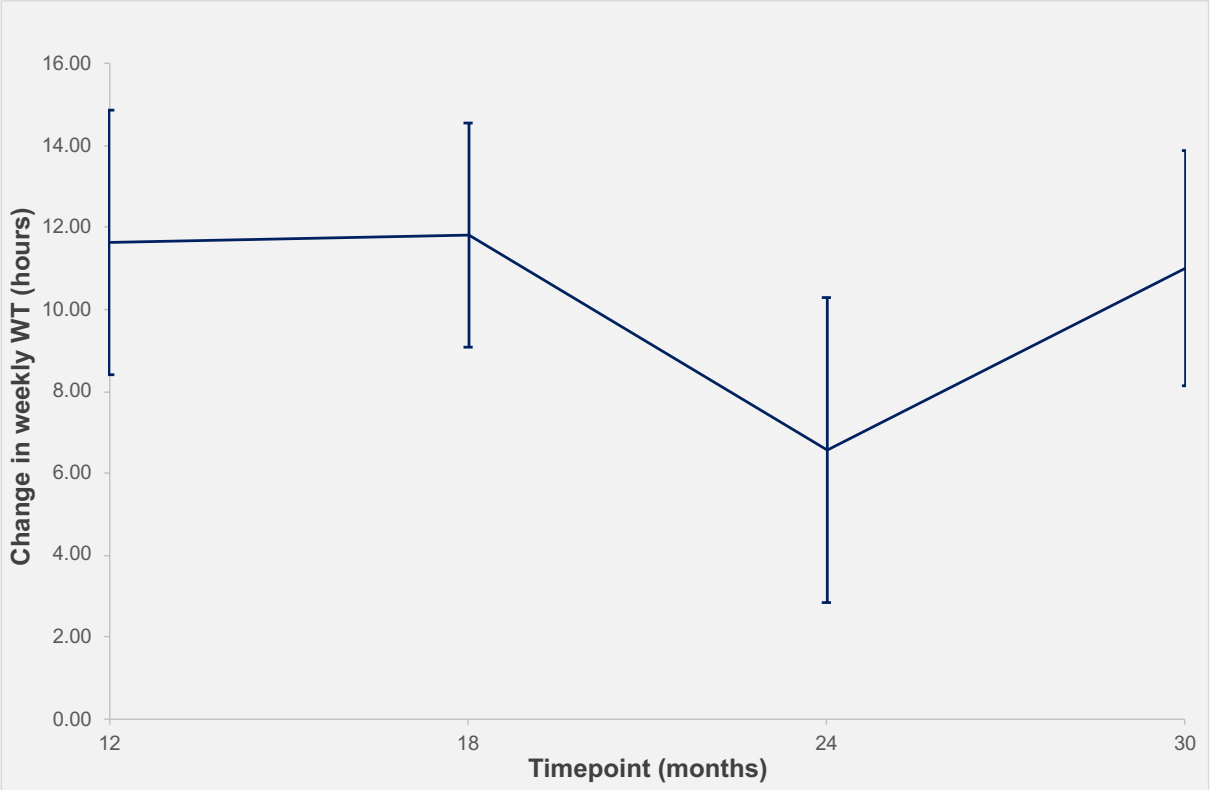

Figure 3.16 Change in typical weekly CL WT (mean ± SEM).

Timepoint (months)	**Weekly CL WT** (hours)
6	59.45 ± 1.64
12	71.09 ± 2.74
18	71.27 ± 3.54
24	66.00 ± 2.44
30	70.45 ± 3.22

Table 3.26 Typical weekly CL WT (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

3.5.2.19 Peripheral refraction (MSE)

Main findings:

- MSE peripheral refraction was relatively myopic in the temporal, nasal, superior, and inferior quadrants in the intervention (see Table 3.27) and control groups (Table 3.28).
- Absolute values for central and peripheral refraction in all four quadrants are detailed in Figures 3.17 to 3.20.

	Relative peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-2.38 ± 0.52	-0.75 ± 0.30	-0.43 ± 0.14	-0.92 ± 0.25
6	-2.62 ± 0.53	-0.51 ± 0.25	-0.71 ± 0.14	-0.57 ± 0.22
18	-2.32 ± 0.61	-0.90 ± 0.30	-1.02 ± 0.34	-0.76 ± 0.20
30	-2.28 ± 0.59	-1.25 ± 0.52	-0.76 ± 0.14	-0.85 ± 0.22
36	-2.29 ± 0.52	-0.77 ± 0.31	-0.58 ± 0.25	-0.66 ± 0.31

Table 3.27 MSE post-cycloplegic relative peripheral refractive error at each visit for the intervention group (mean ± SEM). Intervention period shaded red

	Relative peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-1.26 ± 0.37	-0.91 ± 0.27	-0.69 ± 0.22	-0.93 ± 0.30
6	-1.39 ± 0.33	-1.17 ± 0.28	-0.77 ± 0.22	-0.90 ± 0.31
18	-1.26 ± 0.28	-1.30 ± 0.26	-0.81 ± 0.20	-0.95 ± 0.29
30	-0.98 ± 0.40	-1.16 ± 0.43	-0.77 ± 0.28	-0.75 ± 0.22
36	-0.75 ± 0.40	-0.66 ± 0.39	-0.49 ± 0.19	-0.47 ± 0.22

Table 3.28 MSE post-cycloplegic relative peripheral refractive error at each visit for the control group (mean ± SEM)

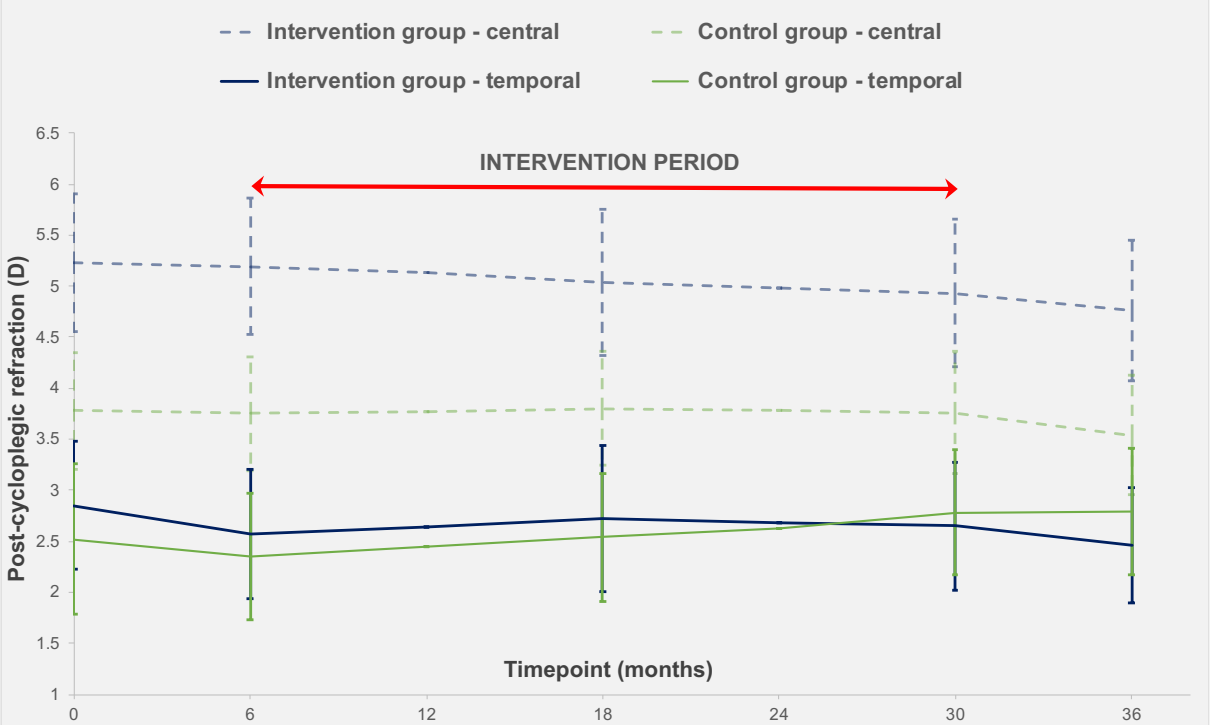

Figure 3.17 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 30° temporally (mean ± SEM)

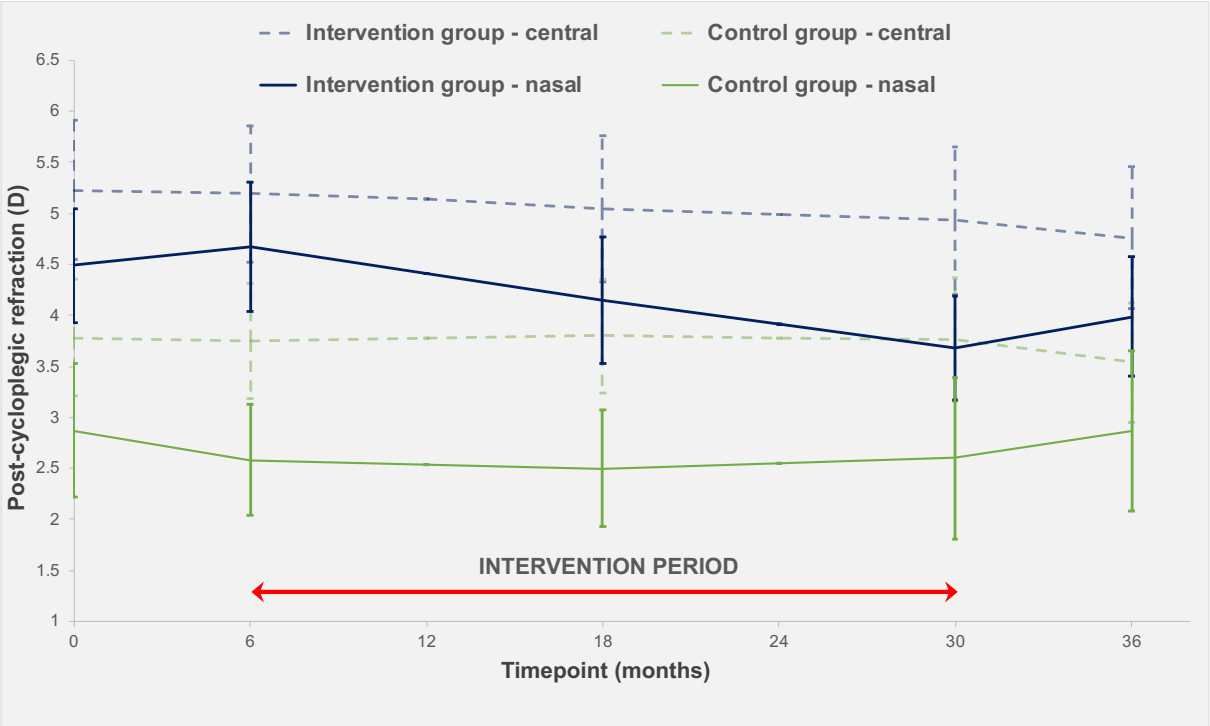

Figure 3.18 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 30° nasally (mean ± SEM)

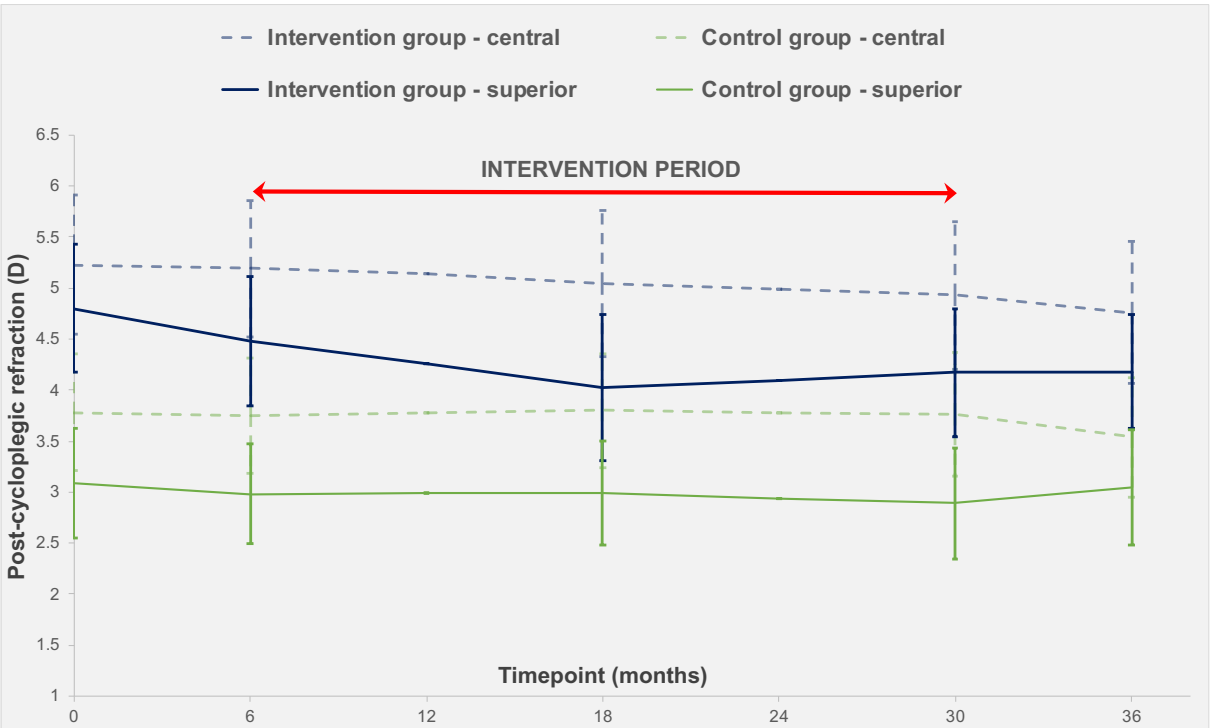

Figure 3.19 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 20° superiorly (mean ± SEM)

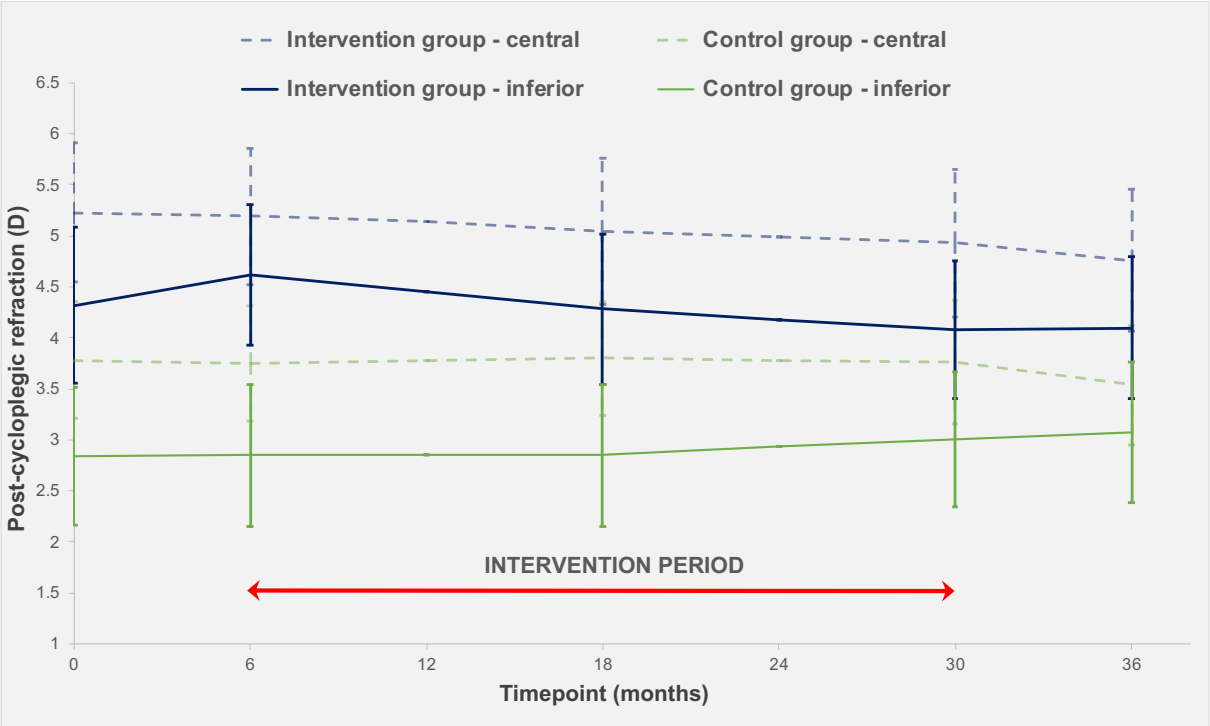

Figure 3.20 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 20° inferiorly (mean ± SEM)

Analysis of the main effects showed that for the intervention group, relative MSE peripheral refraction varied by location ($F_{(3, 30)}$ = 7.006, [Greenhouse-Geisser P = 0.011, Epsilon 0.489]) (See Figure 3.21). A greater degree of relative MSE myopia was found in the temporal quadrant compared to the nasal quadrant (P = 0.023). The temporal quadrant was similar to the superior (P = 0.125) and inferior (P = 0.101) quadrants. Relative MSE peripheral myopia in the nasal quadrant was similar to the superior (P = 1.000) and inferior (P = 1.000) quadrants; this was also the case when comparing the superior quadrant to the inferior quadrant (P = 1.000).

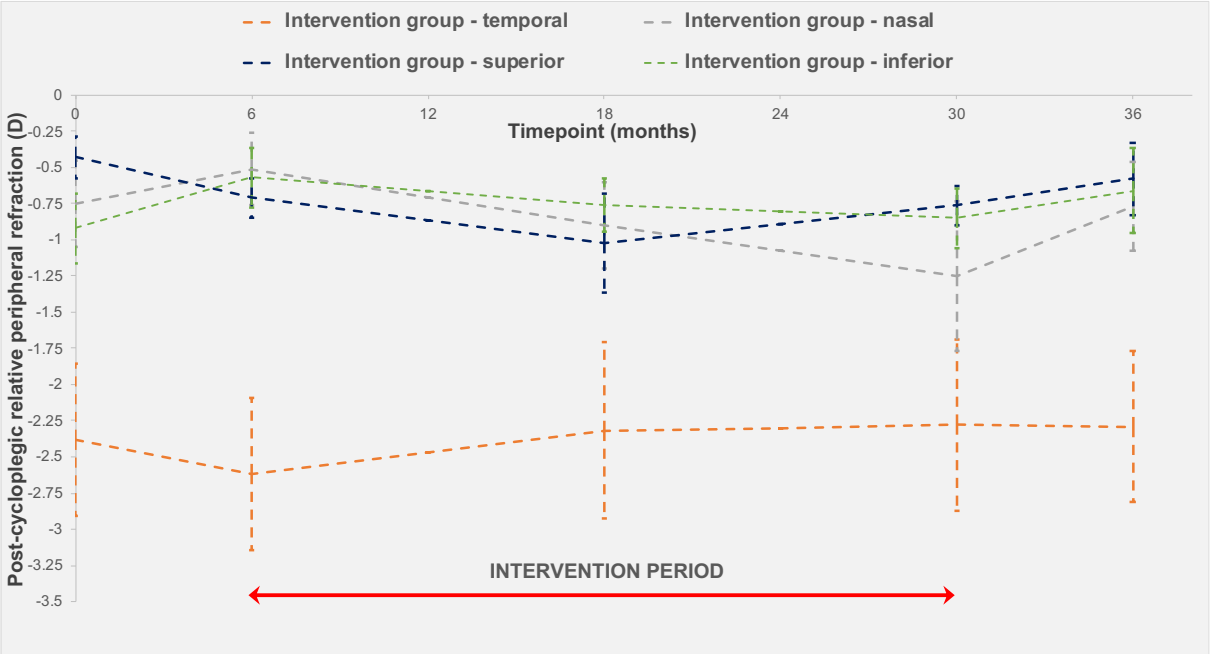

Figure 3.21 MSE post-cycloplegic relative peripheral refractive error at each visit for the intervention group (mean ± SEM)

Analysis of the main effects showed that for the control group, relative peripheral MSE refraction did not vary by location ($F_{(3, 30)}$ = 1.173, P = 0.336) (See Figure 3.22). Relative peripheral MSE myopia in the temporal quadrant was similar to the nasal (P = 1.000), superior (P = 0.731), and inferior (P = 1.000) quadrants; this was also the case when comparing the nasal quadrant to the superior (P = 1.000) and the inferior quadrants (P = 1.000). The superior and inferior quadrants also had similar levels of relative peripheral MSE myopia (P = 1.000).

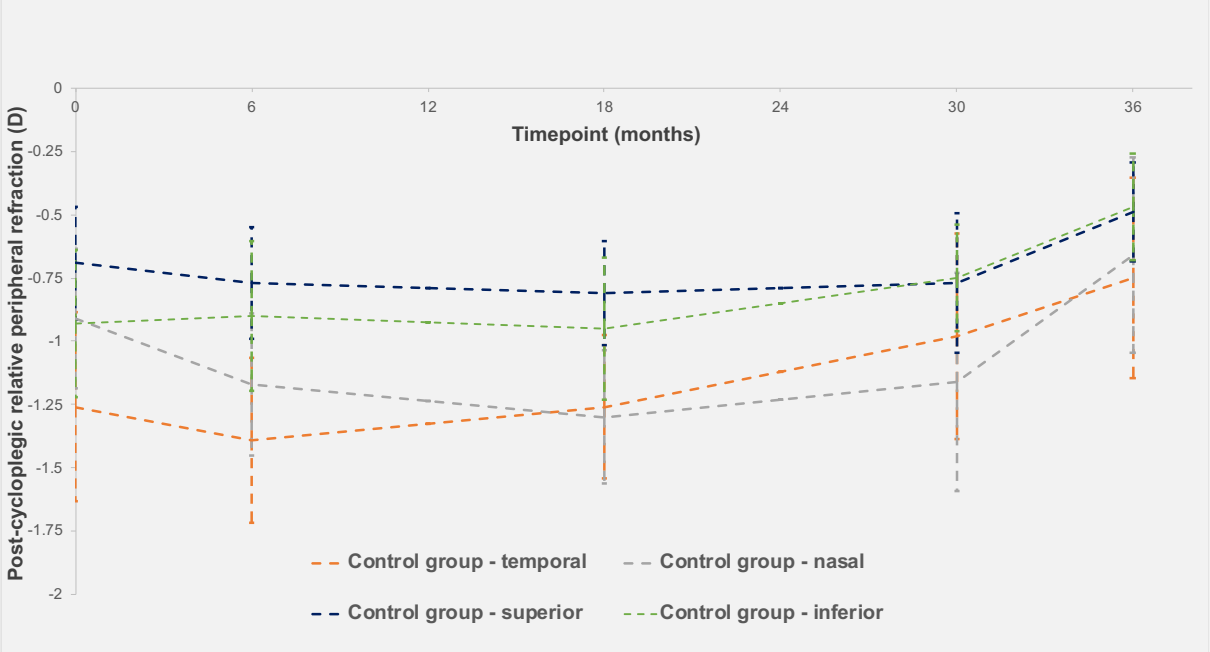

Figure 3.22 MSE post-cycloplegic relative peripheral refractive error at each visit for the control group (mean ± SEM)

Analysis of the main effects showed that relative peripheral MSE refraction in the temporal quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 4.200$, $P = 0.056$) and did not change over time ($F_{(4, 80)} = 1.618$, $P = 0.178$) in either group ($F_{(4, 80)} = 0.415$, $P = 0.797$).

Pairwise comparisons for between-visit analysis (see Figures 3.17 and 3.21, and Table 3.27) showed that for the intervention group, relative peripheral MSE refraction in the temporal quadrant did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figures 3.17 and 3.22, and Table 3.28) showed that for the control group, relative peripheral MSE refraction in the temporal quadrant did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Analysis of the main effects showed that relative peripheral MSE refraction in the nasal quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 0.250$, $P = 0.622$) and did not change over time ($F_{(4, 80)} = 2.046$, $P = 0.096$) in either group ($F_{(4, 80)} = 1.282$, $P = 0.284$).

Pairwise comparisons for between-visit analysis (see Figures 3.18 and 3.21, and Table 3.27) showed that for the intervention group, relative peripheral MSE refraction in the nasal quadrant did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 0.511$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figures 3.18 and 3.22, and Table 3.28) showed that for the control group, relative peripheral MSE refraction in the nasal quadrant did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Analysis of the main effects showed that relative peripheral MSE refraction in the superior quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 0.001$, $P = 0.977$) and did not change over time ($F_{(4, 80)} = 2.044$, $P = 0.096$) in either group ($F_{(4, 80)} = 0.631$ $P = 0.642$).

Pairwise comparisons for between-visit analysis (see Figures 3.19 and 3.21, and Table 3.27) showed that for the intervention group, relative peripheral MSE refraction in the superior quadrant did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figures 3.19 and 3.22, and Table 3.28) showed that for the control group, relative peripheral MSE refraction in the superior quadrant

did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that relative peripheral MSE refraction in the inferior quadrant was similar for the intervention and control groups ($F_{(1, 20)}$ = 0.031, P = 0.863) and did not change over time ($F_{(4, 80)}$ = 1.153, P = 0.338) in either group ($F_{(4, 80)}$ = 0.679 P = 0.608).

Pairwise comparisons for between-visit analysis (see Figures 3.20 and 3.21, and Table 3.27) showed that for the intervention group, relative peripheral MSE refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figures 3.20 and 3.22, and Table 3.28) showed that for the control group, relative peripheral MSE refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

3.5.2.20 Peripheral refraction (J0)

Main findings:

- J0 peripheral refraction for the intervention group varied by location ($F_{(3, 30)} = 47.032$, $P < 0.0005$) (See Figure 3.23). The temporal quadrant showed a greater degree of relative myopia to the nasal ($P < 0.0005$), superior ($P < 0.0005$), and inferior ($P < 0.0005$) quadrants. The nasal quadrant also demonstrated greater relative peripheral myopia compared to the superior ($P = 0.001$) and inferior ($P = 0.041$) quadrants. The superior and inferior quadrants were similar to each other ($P = 1.000$)
- For the control group, analysis of the main effects showed that J0 peripheral refraction varied by location ($F_{(3, 30)} = 13.008$, $P < 0.0005$) (See Figure 3.28). The temporal quadrant was similar to the nasal quadrant ($P = 1.000$) but relatively more myopic than both the superior ($P = 0.006$), and inferior ($P = 0.033$) quadrants. The nasal quadrant also demonstrated greater relative peripheral myopia compared to the superior ($P = 0.004$) and inferior ($P = 0.005$) quadrants. The superior and inferior quadrants were similar to each other ($P = 1.000$).

Analysis of the main effects showed that J0 peripheral refraction in the temporal quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 2.132$, $P = 0.160$) and did not change over time ($F_{(4, 80)} = 0.166$, $P = 0.955$) in either group ($F_{(4, 80)} = 0.692$, $P = 0.600$).

Pairwise comparisons for between-visit analysis (see Figure 3.23 and Table 3.29) showed that for the intervention group, measures in the temporal quadrant did not change from baseline to the 6-month timepoint ($P = 1.000$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 3.24 and Table 3.30) showed that for the control group, measures in the temporal quadrant did not change from baseline to the

6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that J0 peripheral refraction in the nasal quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 4.054$, P = 0.058) and did not change over time ($F_{(4, 80)} = 1.376$, P = 0.250) in either group ($F_{(4, 80)} = 2.309$, P = 0.065).

Pairwise comparisons for between-visit analysis (see Figure 3.23 and Table 3.29) showed that for the intervention group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.24 and Table 3.30) showed that for the control group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.610) and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that J0 peripheral refraction in the superior quadrant were relative more myopic in the control group compared to the intervention group ($F_{(1, 20)} = 7.525$, P = 0.013) and changed over time ($F_{(4, 80)} = 4.613$, P = 0.002) in the intervention group ($F_{(4, 80)} = 2.925$ P = 0.026).

Pairwise comparisons for between-visit analysis (see Figure 3.23 and Table 3.29) showed that for the intervention group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 0.159), 18- and 30-month timepoints (P = 0.285) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.24 and Table 3.30) showed that for the control group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000), and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that J0 peripheral refraction in the inferior quadrant were relative more myopic in the control group compared to the intervention group ($F_{(1, 20)} = 5.297$, P = 0.032) but did not change over time ($F_{(4, 80)} = 0.863$, P = 0.490) in either group ($F_{(4, 80)} = 1.179$ P = 0.327).

Pairwise comparisons for between-visit analysis (see Figure 3.23 and Table 3.29) showed that for the intervention group, measures in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 0.434), nor between the 6- and 18-month timepoints (P = 0.827), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.24 and Table 3.30) showed that for the control group, relative peripheral refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-1.61 ± 0.32	-0.27 ± 0.22	0.43 ± 0.07	0.71 ± 0.13
6	-1.50 ± 0.27	-0.24 ± 0.14	0.51 ± 0.09	0.44 ± 0.23
18	-1.38 ± 0.32	-0.43 ± 0.19	0.91 ± 0.15	0.66 ± 0.14
30	-1.59 ± 0.28	-0.36 ± 0.29	0.64 ± 0.10	0.60 ± 0.16
36	-1.69 ± 0.25	-0.17 ± 0.30	0.58 ± 0.10	0.31 ± 0.25

Table 3.29 J0 post-cycloplegic peripheral refractive error at each visit for the intervention group (mean ± SEM). Intervention period shaded red

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-1.10 ± 0.29	-0.52 ± 0.15	0.13 ± 0.10	0.08 ± 0.19
6	-1.16 ± 0.23	-0.58 ± 0.16	0.26 ± 0.11	-0.04 ± 0.20
18	-1.13 ± 0.23	-0.63 ± 0.14	0.24 ± 0.13	-0.07 ± 0.21
30	-0.98 ± 0.24	-0.90 ± 0.17	0.28 ± 0.14	0.01 ± 0.23
36	-1.02 ± 0.24	-1.08 ± 0.13	0.26 ± 0.16	0.09 ± 0.20

Table 3.30 J0 post-cycloplegic peripheral refractive error at each visit for the control group (mean ± SEM)

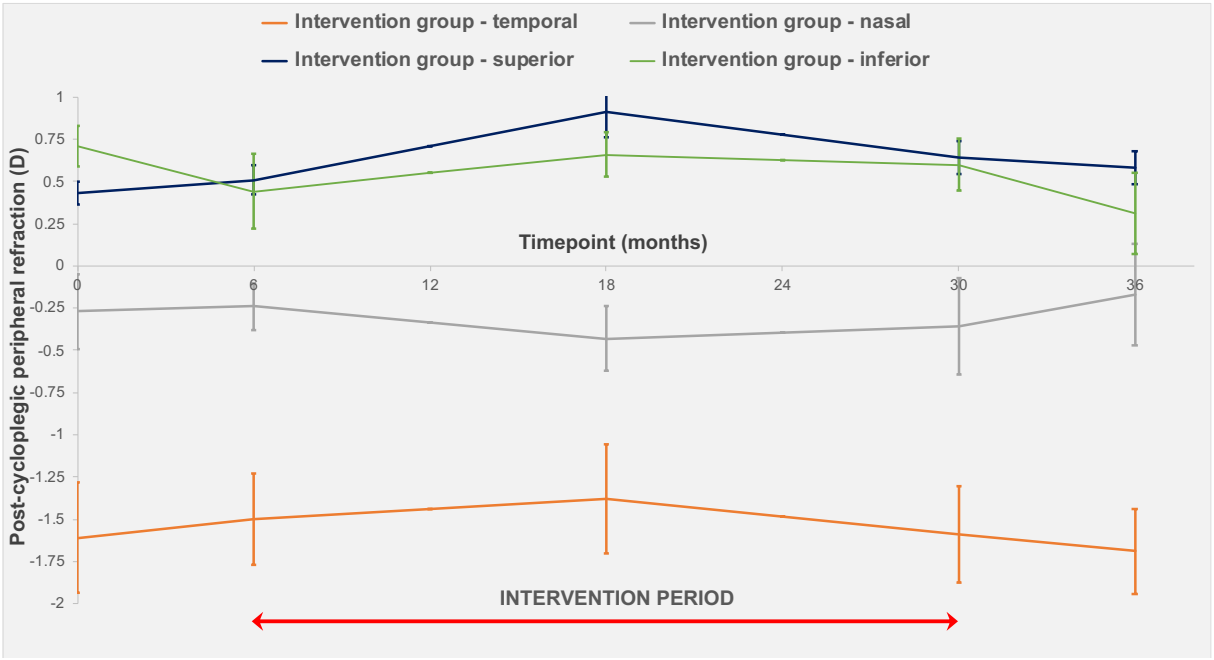

Figure 3.23 J0 post-cycloplegic peripheral refractive error at each visit for the intervention group (mean ± SEM)

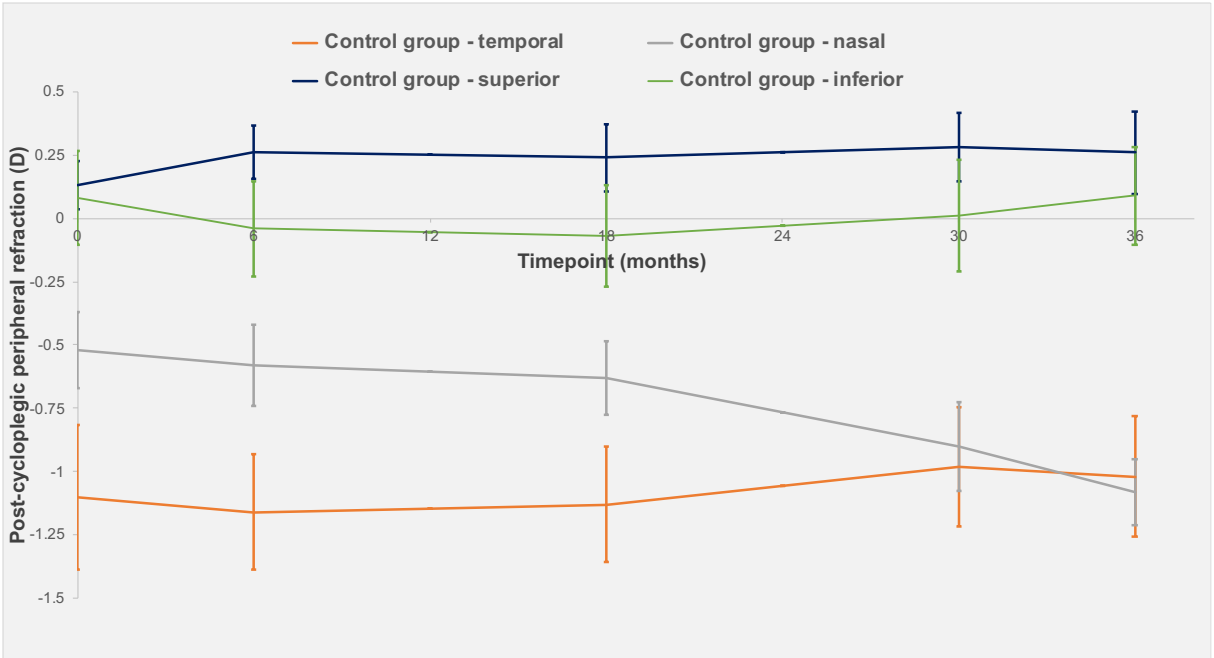

Figure 3.24 J0 post-cycloplegic peripheral refractive error at each visit for the control group (mean ± SEM)

3.5.2.21 Peripheral refraction (J45)

Main findings:

- J45 peripheral refraction for the intervention group varied by location ($F_{(3, 30)} = 4.073$, P = 0.015) (See Figure 3.25). The temporal quadrant was similar to the nasal (P = 1.000), superior (P = 0.261), and inferior (P = 1.000) quadrants. The nasal quadrant was relatively more myopic than the superior quadrant (P = 0.030) but similar to the inferior quadrant (P = 1.000). However, the inferior quadrant demonstrated a greater degree of relative myopia compared to the superior quadrant (P = 0.008)
- For the control group, analysis of the main effects showed that J45 peripheral refraction did not vary by location ($F_{(3, 30)} = 1.252$, P = 0.308) (See Figure 3.26). The temporal quadrant was similar to the nasal (P = 1.000), superior (P = 0.739), and inferior (P = 1.000) quadrants. The nasal quadrant was also similar to the superior (P = 1.000) and inferior (P = 1.000) quadrants. The superior and inferior quadrants were also comparable to each other (P = 0.088).

Analysis of the main effects showed that J45 peripheral refraction in the temporal quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 0.004$, P = 0.951) and did not change over time ($F_{(4, 80)} = 2.077$, P = 0.091) in either group ($F_{(4, 80)} = 1.188$, P = 0.322).

Pairwise comparisons for between-visit analysis (see Figure 3.25 and Table 3.31) showed that for the intervention group, measures in the temporal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 0.550), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.26 and Table 3.32) showed that for the control group, measures in the temporal quadrant did not change from baseline to the

6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that J45 peripheral refraction in the nasal quadrant was similar for the intervention and control groups ($F_{(1, 20)}$ = 0.002, P = 0.963) and did not change over time ($F_{(4, 80)}$ = 1.158, P = 0.336) in either group ($F_{(4, 80)}$ = 0.888, P = 0.475).

Pairwise comparisons for between-visit analysis (see Figure 3.25 and Table 3.31) showed that for the intervention group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 0.916), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.26 and Table 3.32) showed that for the control group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.610) and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that J45 peripheral refraction in the superior quadrant were relative more myopic in the control group compared to the intervention group ($F_{(1, 20)}$ = 11.422, P = 0.003) and changed over time ($F_{(4, 80)}$ = 4.843, P = 0.002) in both groups ($F_{(4, 80)}$ = 1.909 P = 0.117).

Pairwise comparisons for between-visit analysis (see Figure 3.25 and Table 3.31) showed that for the intervention group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 0.138), nor between the 6- and 18-month timepoints (P = 0.108), 18- and 30-month timepoints (P = 0.570), and the 30- and 36-month timepoints (P = 0.723).

Pairwise comparisons for between-visit analysis (see Figure 3.26 and Table 3.32) showed that for the control group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Analysis of the main effects showed that J45 peripheral refraction in the inferior quadrant was similar for the intervention and control groups ($F_{(1, 20)} = 0.493$, P = 0.491) and did not change over time ($F_{(4, 80)} = 0.498$, P = 0.737) in either group ($F_{(4, 80)} = 1.052$, P = 0.386).

Pairwise comparisons for between-visit analysis (see Figure 3.25 and Table 3.31) showed that for the intervention group, measures in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.363) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 3.26 and Table 3.32) showed that for the control group, relative peripheral refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-0.20 ± 0.21	0.18 ± 0.16	0.34 ± 0.13	-0.10 ± 0.13
6	-0.24 ± 0.25	0.02 ± 0.09	0.55 ± 0.08	-0.07 ± 0.09
18	0.18 ± 0.16	-0.06 ± 0.14	0.42 ± 0.10	-0.12 ± 0.08
30	0.08 ± 0.16	-0.12 ± 0.18	0.34 ± 0.09	-0.29 ± 0.11
36	-0.01 ± 0.16	-0.10 ± 0.16	0.26 ± 0.08	-0.13 ± 0.16

Table 3.31 J45 post-cycloplegic peripheral refractive error at each visit for the intervention group (mean ± SEM). Intervention period shaded red

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-0.10 ± 0.10	-0.01 ± 0.06	0.14 ± 0.05	-0.12 ± 0.05
6	-0.04 ± 0.10	0.00 ± 0.06	0.13 ± 0.05	-0.12 ± 0.09
18	-0.06 ± 0.06	0.02 ± 0.06	0.07 ± 0.04	-0.09 ± 0.05
30	0.08 ± 0.07	-0.12 ± 0.15	0.01 ± 0.04	-0.06 ± 0.06
36	-0.01 ± 0.06	0.06 ± 0.10	0.05 ± 0.05	-0.01 ± 0.07

Table 3.32 J45 post-cycloplegic peripheral refractive error at each visit for the control group (mean ± SEM)

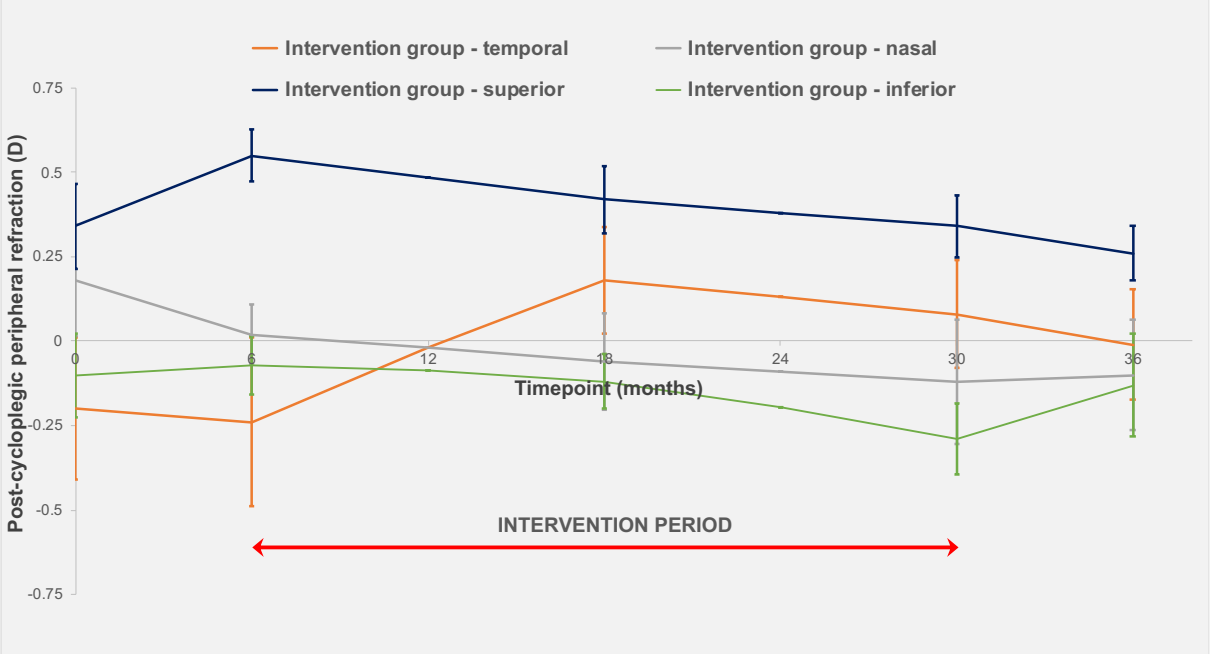

Figure 3.25 J45 post-cycloplegic peripheral refractive error at each visit for the intervention group (mean ± SEM)

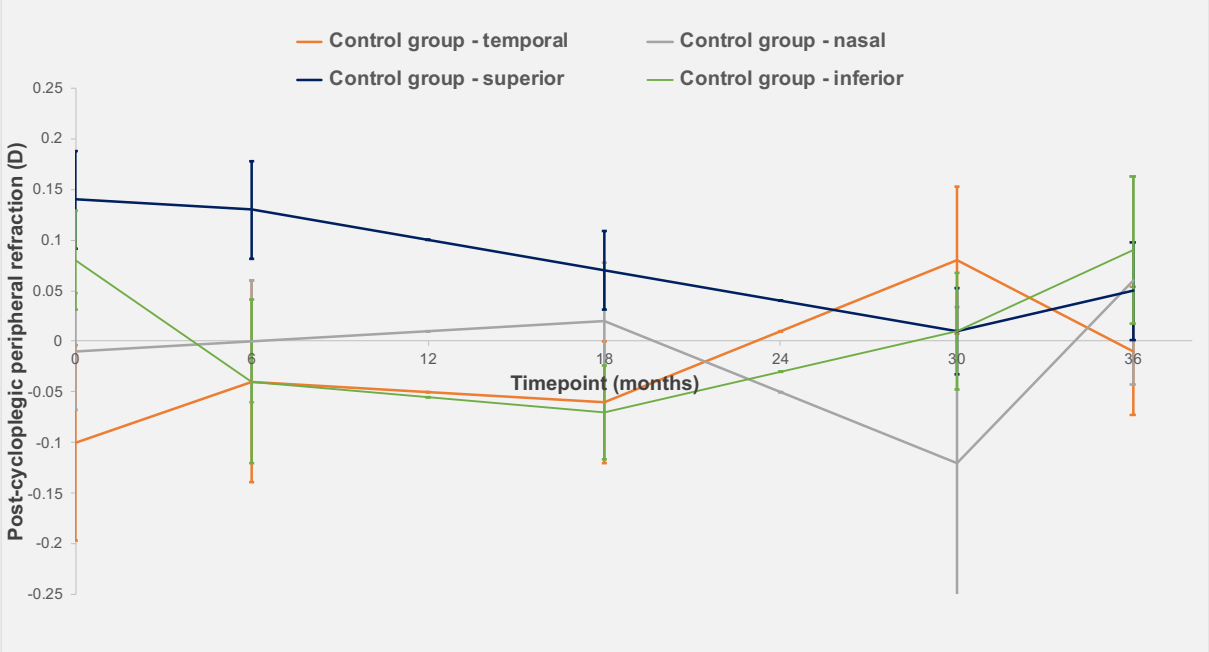

Figure 3.26 J45 post-cycloplegic peripheral refractive error at each visit for the control group (mean ± SEM)

3.5.2.22 Relative peripheral refraction with CL *in situ*

Main findings:

- Non-cycloplegic peripheral refraction with CL correction *in situ* demonstrated relative hyperopia in all four quadrants although the magnitude varied by location ($F_{(3, 30)}$ = 6.991, P = 0.001).

Pairwise comparisons (see Figure 3.27 and Table 3.33) showed that the temporal quadrant was similar to the nasal (P = 1.000), superior (P = 0.165), and inferior quadrants (P = 0.239), respectively. The nasal quadrant demonstrated a greater degree of relative hyperopia compared to the superior (P = 0.013) and inferior quadrants (P = 0.016), while the superior and inferior quadrants were similar to each other (P = 1.000).

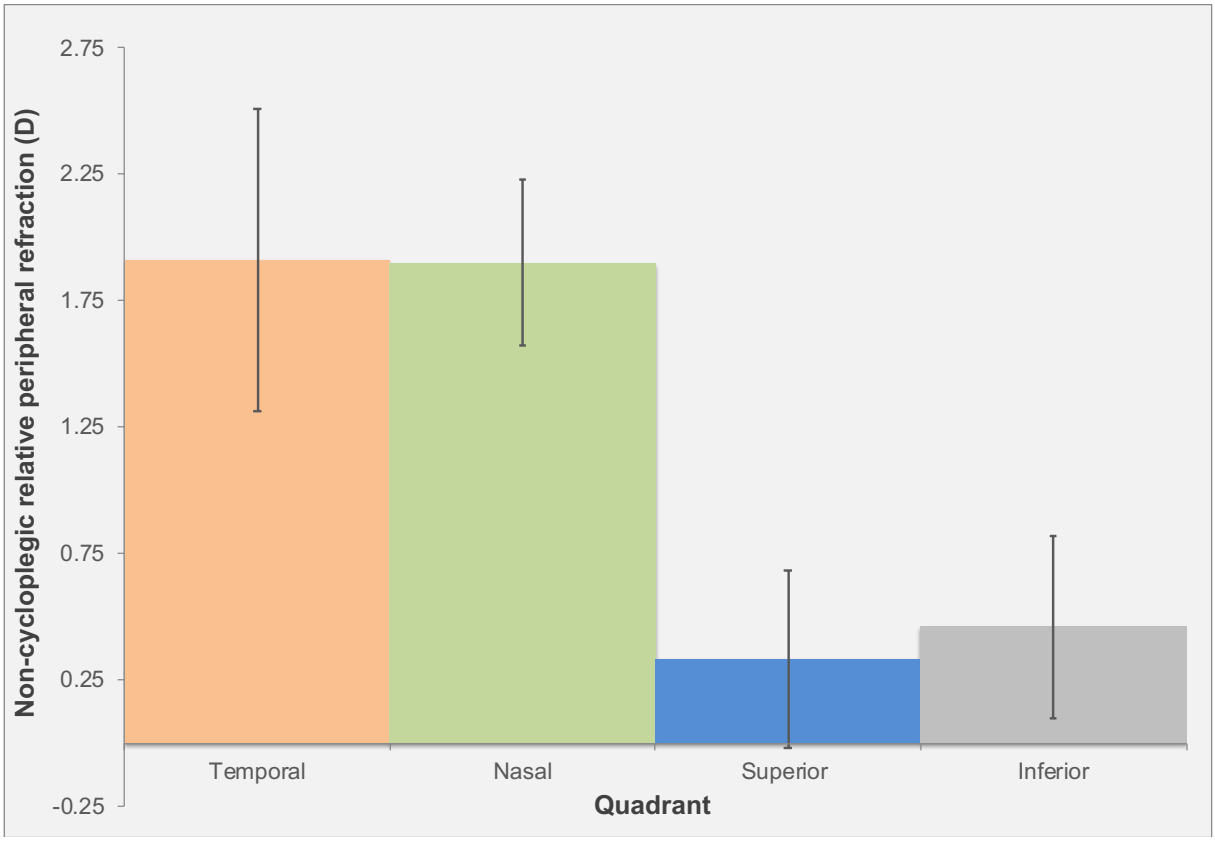

Figure 3.27 MSE non-cycloplegic relative peripheral refraction with CL correction *in situ* (mean ± SEM)

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
12	1.91 ± 0.60	1.90 ± 0.33	0.33 ± 0.35	0.46 ± 0.36

Table 3.33 MSE non-cycloplegic relative peripheral refraction with CL correction *in situ* (mean ± SEM)

3.6 Discussion

This clinical trial has shown for the first time that the imposition of RPHD using MF CLs, can accelerate axial growth in children with isohyperopia. Participants in the control arm of the study demonstrated axial growth rates that were similar to other longitudinal observations in UK children with hyperopia (Breslin *et al*., 2013). Crucially, the axial growth rates seen in controls were significantly outpaced by participants receiving the intervention over the two-year period of wearing MF CLs. In the 6 months prior to receiving the intervention, axial growth rates for the control and intervention groups were the same. Similarly, once CL wear was

ceased during the final 6 months of the trial, the faster growth rates experienced by the intervention group during the two-year period of wearing CLs, reverted to a pace that matched the control group.

As participants in the intervention arm of the trial experienced a faster rate of axial growth than controls, it would be expected that a decrease in hyperopia would also occur. However, although the overall trend showed a greater reduction in post-cycloplegic refractive error in those receiving the intervention compared to the control group, this did not reach a level of significance nor achieve adequate statistical power. Nevertheless, the mean reduction in refractive error for participants receiving the intervention was almost double the decrease in the control group at 0.47 D and 0.24 D, respectively, which offers optimism for further research in this area. Unlike AL, post-cycloplegic refraction was only measured at 5 out of 7 timepoints. Although capturing data at these 2 additional timepoints would have increased statistical power, this has to be balanced against placing additional burden upon participants, which could in turn, affect rates of attrition. Given the effect size, it is estimated that to achieve statistical power at 80% over 5 data collection points, a sample size of 23 participants per group would be required.

In terms of secondary outcome measures, the results were largely in keeping with expectation. For parameters related to vision, unaided DV and spectacle DVA were similar for the intervention and control groups and did not change; this is unsurprising given the age of participants and relatively small reduction in refractive error over the period of the trial. Both DVA and NVA were better in spectacles than CLs, which is line with previous findings when comparing SV with MF CL correction (Sha *et al*., 2016). Nevertheless, VA improved over time with both forms of correction at distance and near. Taking into account the mean DVA values, there was greater improvement over time with CLs compared to spectacles which is likely to reflect a period of adaptation. Although stereoacuity with spectacles was similar for both groups and did not change over time, in the intervention group it was poorer with CL correction

compared to spectacles and failed to improve during the two-year period of CL wear; this is in contrast to findings from earlier work demonstrating that stereoacuity appears to be preserved in MF CL wear compared to SV correction, albeit in a presbyopic cohort (Ferrer-Blasco and Madrid-Costa, 2011). From the start, CS was better in the control group than the intervention group and did not change over time. Encouragingly, CS was similar with spectacle and CL correction. For measures of anterior eye parameters, as with previous refractive modulation work in myopes (Sankaridurg *et al*., 2001; Lam *et al*., 2014; Aller *et al*., 2016), CC did not change over time in either group. ACD changed over time in both the control and intervention groups by a comparable amount; this suggests that the greater AL change observed in the intervention group is attributable primarily to VCD growth. Evaluation of accommodation revealed that lag with spectacles was similar for intervention and control participants and increased over time; this is surprising, particularly given that NVA *improved* over time in both groups. Perhaps of greater relevance is that accommodative lag was greater with CL correction than spectacle correction, which may reflect that hyperopes would be expected to converge less through the former. Given that accommodative lag has been implicated in myopia progression (Mutti *et al*., 2006; Chakraborty *et al*., 2020) it is plausible that lag may be a factor in driving axial growth in CL-wearing participants in the present study. It is noteworthy that central CL power decreased significantly over time although this measure was determined under non-cycloplegic conditions. Nevertheless, the mean power reduction of 0.38 D over the two-year intervention period was in broad agreement with the reduction in spectacle refraction recorded under cycloplegia in these participants over the same time period.

In line with previous work, peripheral refraction was relatively myopic in all four quadrants (Atchison *et al*., 2005; Gilmartin *et al*., 2005; Charman and Radhakrishnan, 2010; Atchison and Charman, 2011; Schmid, 2011; Verkicharla *et al*., 2012). Importantly, while wearing the intervention, relative peripheral refraction was hyperopic in all four quadrants, demonstrating merit in using centre-near CLs to expose the peripheral retina to hyperopic defocus. There remains conjecture regarding the role of peripheral hyperopic defocus in the progression of

myopia (Charman and Radhakrishnan, 2010; Mutti *et al*., 2019). As outlined earlier (see Sections 1.5.3 and 1.5.4), studies evaluating the benefit of spectacle lenses that manipulate peripheral defocus in myopes report inconsistent results whereas soft multifocal contact lenses targeting a similar objective, are, with a moderate certainty of evidence, capable of slowing axial growth in this refractive cohort. Further, it is proposed that customising the CL design with the express purpose of achieving a greater shift in peripheral defocus may be of value, although further evidence using this approach is required (Nemeth *et al*., 2021). At a simple level, it is clear that ocular shape and peripheral characteristics are different between refractive subtypes. Specifically, myopic eyes tend to be relatively prolate, exhibit relative peripheral hyperopia with a slowing of axial growth in response to the imposition of myopic defocus. Conversely, hyperopes have a more oblate shape, are relatively myopic in the periphery, and on the basis of the present work, demonstrate accelerated axial growth in response to the imposition of RPHD. Indeed, the outcome witnessed in the intervention group offers credibility to the hypothesis that exposing the hyperopic eye to RPHD may provide the necessary signal to stimulate axial growth in children.

Participants in the intervention arm of the study proved to be adept at handling and maintaining their CLs which is in keeping with earlier work on the safety of CLs in children (Bullimore, 2017; Chalmers *et al*., 2021). Two participants failed to handle CLs adequately and did not proceed; interestingly, both were teenagers rather than younger children. Almost all of the participants that successfully transitioned the application and removal phase of the study continued to wear CLs for the full two years of intervention with just one being withdrawn due to poor compliance.

In future work, it would be important to establish if a greater effect can be achieved through earlier intervention. Exposing the hyperopic eye to peripheral hyperopic defocus at a younger age when natural growth is faster may yield better results as well as potentially improving the visual outcome, for instance, measures of VA and stereopsis. Nevertheless, it is important to recognise the difficulties of recruiting hyperopes, particularly at a young age. Given the nature

of refractive error distribution, hyperopes are relatively scarce in comparison to their myopic counterparts. Furthermore, in the absence of amblyopia, many isohyperopes may pass vision screening protocols as they enter the school system and remain unidentified. For those who fail vision screening, many are diverted to secondary care for several years making recruitment at a young age more difficult in a primary care setting.

In terms of the main objective, the results demonstrating the effect of the intervention on axial growth is encouraging. However, it is important to recognise the limitation of this work in terms of refractive error outcome, which lacked statistical power and did not reach a significant level. Further work would benefit from a larger scale study undertaken as a double-masked, randomised control trial. An additional limitation is the reporting of CL compliance, specifically with respect to wearing times as these were self-reported by participants. Still, anecdotally, the majority of participants were disappointed to reach the end of the intervention period as they were keen to continue with CL wear, which suggests that in most cases, compliance was high.

Inclusion of amblyopes formed part of the study protocol to ensure that participants were drawn from a representative sample. Nevertheless, to disentangle this potential confounding variable from the main dataset, further analysis with the exclusion of amblyopic participants was undertaken for the primary outcome measures. Interestingly, this reanalysis did not impact upon the findings for AL or refractive error, suggesting that the effect of the intervention is not influenced by the presence of amblyopia.

Having identified a mechanism to modulate axial growth holds promise for hyperopes and provides a platform for an extension to this work. The ability to accelerate axial growth in hyperopes may help to decrease the risk of ocular comorbidities associated with small globes as well as reduce the burden of refractive error in these children. Furthermore, MF CLs in children with isohyperopia appear to be well tolerated both from a handling and wearing perspective as well as providing adequate visual performance.

4.0 Effect of peripheral defocus on axial growth and refractive error in children with anisohyperopia

4.1 Introduction

In Chapter 3, the impact of imposing RPHD in isohyperopes using soft centre-near BF CLs was explored. The aim with this approach was to attempt to accelerate axial growth bilaterally to reduce the overall level of refractive error. A natural extension to this work is to consider a similar method with anisohyperopes. The aim here would be to accelerate axial growth unilaterally, that is to say, in the more hyperopic eye, to reduce the overall level of anisometropia thereby providing a platform for a more natural binocular status. In addition to the risk of amblyopia and strabismus in anisohyperopia, accelerating the growth of the smaller eye could help to mitigate for conditions with known association to eyes of short axial length including angle closure glaucoma, early AMD, and vascular events, such as branch and central retinal vein occlusion.

Take for example, a child with the following refractive error: R +5.00 D L +2.50 D. In this case, the child could be fitted with a centre-near CL with a prescription of +3.00 D add +2.00 D in the right eye; this specification would provide 5.00 D of refractive correction in the central portion, while imposing 2.00 D of relative hyperopia in the periphery. In the left eye, a SV CL could be used with a power of +2.50 D.

To date, there has been no attempt to impose RPHD to modulate refractive error and axial growth in human anisohyperopes.

4.2 Objective

The objective of this clinical trial was to establish whether axial eye growth and refractive error could be modified in an anisohyperopic cohort by imposing relative hyperopic defocus using a

MF CL in the more hyperopic eye. The aim here was to reduce the interocular difference in refractive error thereby mitigating for the effects of anisohyperopia.

4.3 Methods

Sample size calculation indicated that 11 participants would be required to achieve 80% power for an effect size of 0.25 at a significance level of 5% using a mixed factor repeated measures ANOVA design (G*Power 3.1, Franz Faul, Universität Kiel, Germany). The aim was to recruit 13 participants to achieve statistical power and allow for attrition. Suitable candidates for the 3-year study were recruited by displaying notices at the research venues. Potential participants were also sourced through a database search at the research venues to identify individuals that met the age and refractive error inclusion criteria.

During the 6- to 30-month timepoints, participants were fitted with a centre-near MF soft CL in their more hyperopic eye, while the fellow eye was fitted with a SV CL if required (see Chapter 2.11). Participants aged between 8 and <16 years-of-age were recruited for the study.

Prior to commencing the research, ethical approval was obtained from both the NHS (see Appendix 1) and Aston University's Research Ethics Committees (see Appendix 2) with the study designed to follow the tenets of the Declaration of Helsinki. Each participant, and their parent or guardian where appropriate, was given detailed information regarding the nature of the study, both verbally and in written form; this allowed informed consent and assent to take place prior to participation. The participants were required to complete a short questionnaire to ensure that they met the inclusion criteria (see Appendix 3). The programme of research was registered as a clinical trial: ClinicalTrials.gov NCT02686879. The participant's general practitioner was notified of their inclusion in the study (see Appendix 4).

Inclusion criteria were as follows:

- Aged between 8 and < 16 years-of-age at the initial examination

- Parents must have read, understood and signed the informed consent form (see Appendix 5)
- Participants must have read, understood and signed the consent or assent form as appropriate (see Appendix 6 and 7)
- Participants agreed to wear the prescribed CLs for a minimum of 10 hours per day, at least 6 days per week for the 2-year duration of the intervention period
- Be in good general health with no contraindications to CL wear
- Maximum manifest spherical refractive error of +6.00 D
- Maximum manifest cylindrical refractive error of -1.00 D
- Manifest anisometropia of >1.00 D (mean spherical error)
- Minimum mean spherical refractive error of +2.00D in the more hyperopic eye for inclusion in the intervention group
- Be competent at handling CLs and understand the instructions given to ensure safe wear.

Exclusion criteria were as follows:

- Previous CL wear
- Participating in another clinical study
- Regular use of medication to treat ocular conditions
- Current use of systemic medication that could impact upon successful CL wear or affect focusing ability
- Known ocular or systemic disease
- Findings identified during CL assessment that would preclude CL wear
- Participants who were not able to provide informed consent without the aid of an interpreter due to lack of funding available for the provision of this facility.

A summary of the procedures conducted at each visit are detailed below and in Table 4.1. Visits 1 to 7 were undertaken at 6-monthly intervals (± 2 weeks) for all participants. For

participants in the intervention group, CL fitting, CL aftercare at 1 to 2 weeks after the initial fitting and CL aftercare 1 month after the first aftercare were also scheduled. At visit 1, all participants completed a background questionnaire (see Appendix 3) to elicit detail of previous ocular history and general health status. At visits 2 to 8, all participants completed a follow-up questionnaire (see Appendix 8) to elicit detail of any changes to ocular history and general health status.

Procedure	Visit 1	Visit 2a	Visit 2b	Visit 2c	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Unaided DV	✅	✅			✅	✅	✅	✅	✅
Subjective refraction	✅	✅			✅	✅	✅	✅	✅
DVA	✅	✅			✅	✅	✅	✅	✅
NVA	✅	✅			✅	✅	✅	✅	✅
Lag of accommodation	✅	✅			✅	✅	✅	✅	✅
Lag with CL *in situ*					✅		✅		
Amplitude of accommodation	✅	✅			✅	✅	✅	✅	✅
Stereoacuity	✅	✅			✅	✅	✅	✅	✅
Stereoacuity with CL in situ					✅		✅		
Cover test	✅	✅			✅	✅	✅	✅	✅
CC	✅	✅			✅	✅	✅	✅	✅
Slit lamp examination	✅	✅				✅		✅	✅
AL	✅	✅			✅	✅	✅	✅	✅
IOP	✅	✅				✅		✅	✅
Post-cycloplegic autorefraction	✅	✅				✅		✅	✅
Peripheral refraction	✅	✅				✅		✅	✅
CS		✅						✅	✅
CS with CL *in situ*			✅					✅	
ACD	✅	✅			✅			✅	✅
Pupil size					✅				

CL fitting		✅							
CL aftercare			✅	✅	✅	✅	✅	✅	
Central refraction with CL *in situ*					✅				
Peripheral refraction with CL *in situ*					✅				

Table 4.1 Procedures undertaken for all participants at each visit

4.4 Statistical analysis

All data were analysed using the commercially available software, SPSS, *v*. 25, IBM, New York, U.S.A. Data were examined with mixed factor repeated measures analysis of variance (ANOVA) with one within-subject factor (time) and one between-subject factor (intervention or control). Bonferroni correction was applied and a significance level of $\alpha < 0.05$ used throughout (Armstrong *et al*., 2011; Armstrong *et al*., 2002).

4.5 Results

Data were analysed to compare the primary (see 4.5.1) and secondary (see 4.5.2) outcome measures for the intervention eye group and control eye group. In total, 11 participants were recruited, all of whom completed the trial and comprised of 8 females and 3 males with an age range at baseline of 8.25-13.42 years (mean 10.56 SD 1.43 years); these data were normally distributed (Kolmogorov-Smirnov, Z = 0.179, P = 0.200). A summary of descriptive data from questionnaires undertaken at each visit is detailed in Table 4.2.

	Visit 1		**Follow up visits**
Participant	**History**	**Medication**	**Notes**
1	Full time spectacles at 2 years of age. Occlusion therapy until 3 years of age.	Nil	
2	Full time spectacles at 5 years of age	Nil	
3	Full time spectacles at 5 years of age	Nil	Cetirizine during hay fever seasons
4	Full time spectacles at 3 years of age	Nil	

5	Full time spectacles at 6 years of age	Nil	
6	Full time spectacles at 7 years of age	Nil	
7	Full time spectacles at 4 years of age	Nil	
8	Full time spectacles at 4 years of age. Occlusion therapy until 5 years of age.	Nil	
9	Full time spectacles at 5 years of age	Salbutamol	Cetirizine during hay fever seasons
10	Full time spectacles at 7 years of age	Nil	
11	Full time spectacles at 4 years of age	Nil	

Table 4.2 Summary of key information from questionnaires

4.5.1 Primary outcome measures

4.5.1.1 Axial growth

Main findings:

- AL changed over time ($F_{(6, 60)} = 14.808$, $P < 0.0005$) for the control eye group but not the intervention eye group ($F_{(6, 60)} = 2.609$, $P = 0.026$)
- Observed power was 0.816.

Pairwise comparisons for between-visit analysis (see Figure 4.1 and Table 4.3) showed that for the intervention eye group, AL did not change from baseline to the 6-month timepoint ($P = 1.000$). When the intervention was introduced, AL did not change between the 6- and 12-month timepoints ($P = 0.452$) but did change between the 12- and 18-month timepoints ($P = 0.049$). There was no change in AL between the 18- and 24-month timepoints ($P = 0.700$) or the 24- and 30-month timepoints ($P = 1.000$). Once the intervention was withdrawn, AL did not change between the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 4.1 and Table 4.3) showed that for the control eye group, AL did not change from baseline to the 6-month timepoint ($P = 0.052$),

nor between the 6- and 12-month timepoints (P = 1.000) but did change between the 12- and 18-month timepoints (P = 0.003). There was no change in AL between the 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 0.820) and the 30- and 36-month timepoints (P = 1.000).

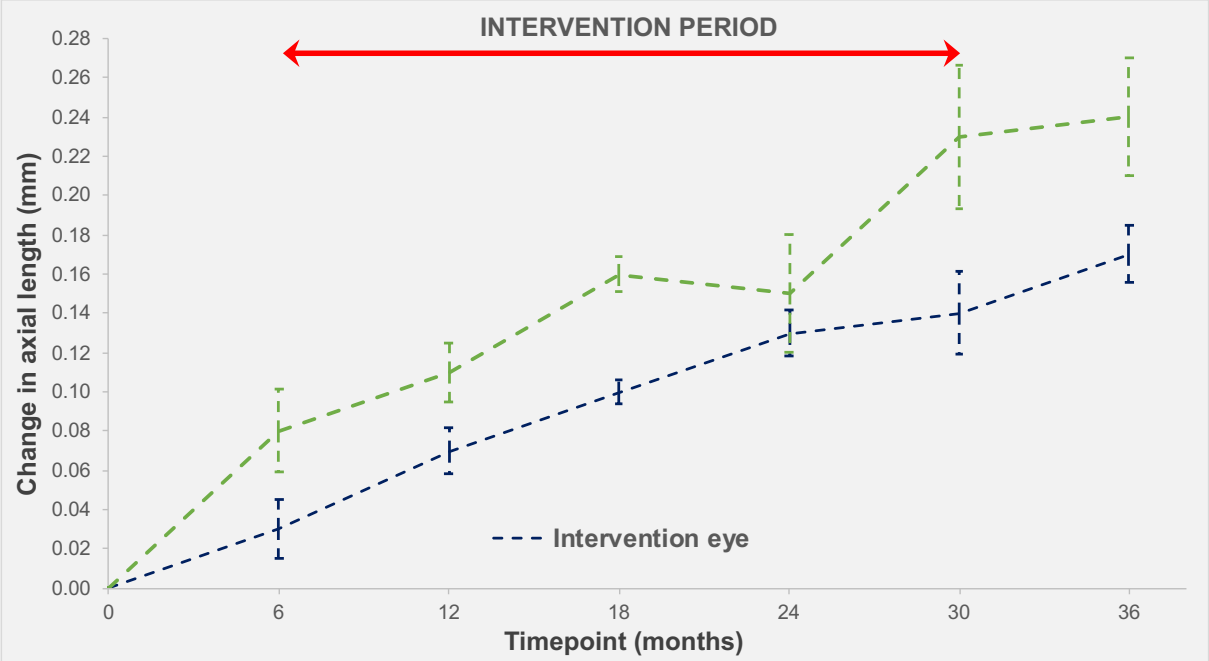

Figure 4.1 Change in AL (mean ± SEM)

Timepoint (months)	**AL** (mm)	
Baseline	21.67 ± 0.20	22.19 ± 0.21
6	21.70 ± 0.19	22.27 ± 0.21
12	21.74 ± 0.19	22.30 ± 0.21
18	21.77 ± 0.19	22.35 ± 0.21
24	21.80 ± 0.18	22.34 ± 0.20
30	21.81 ± 0.19	22.42 ± 0.22
36	21.84 ± 0.19	22.43 ± 0.22
	Intervention (n = 11)	**Control** (n = 11)

Table 4.3 AL at each visit (mean ± SEM). Intervention period shaded red

4.5.1.2 Post-cycloplegic refractive error

Main findings:

- Post-cycloplegic MSE refractive error decreased over time ($F_{(4, 40)} = 4.601$, $P = 0.004$) for both the intervention eye group and the control eye group ($F_{(4, 40)} = 0.318$, $P = 0.864$)
- Observed power was 0.114 and partial η^2 was 0.031.

Pairwise comparisons for between-visit analysis (see Figure 4.2 and Table 4.4) showed that for the intervention eye group, post-cycloplegic MSE refractive error did not change from baseline to the 6-month timepoint (P = 0.318), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.2 and Table 4.4) showed that for the control eye group, post-cycloplegic MSE refractive error did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 0.076), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

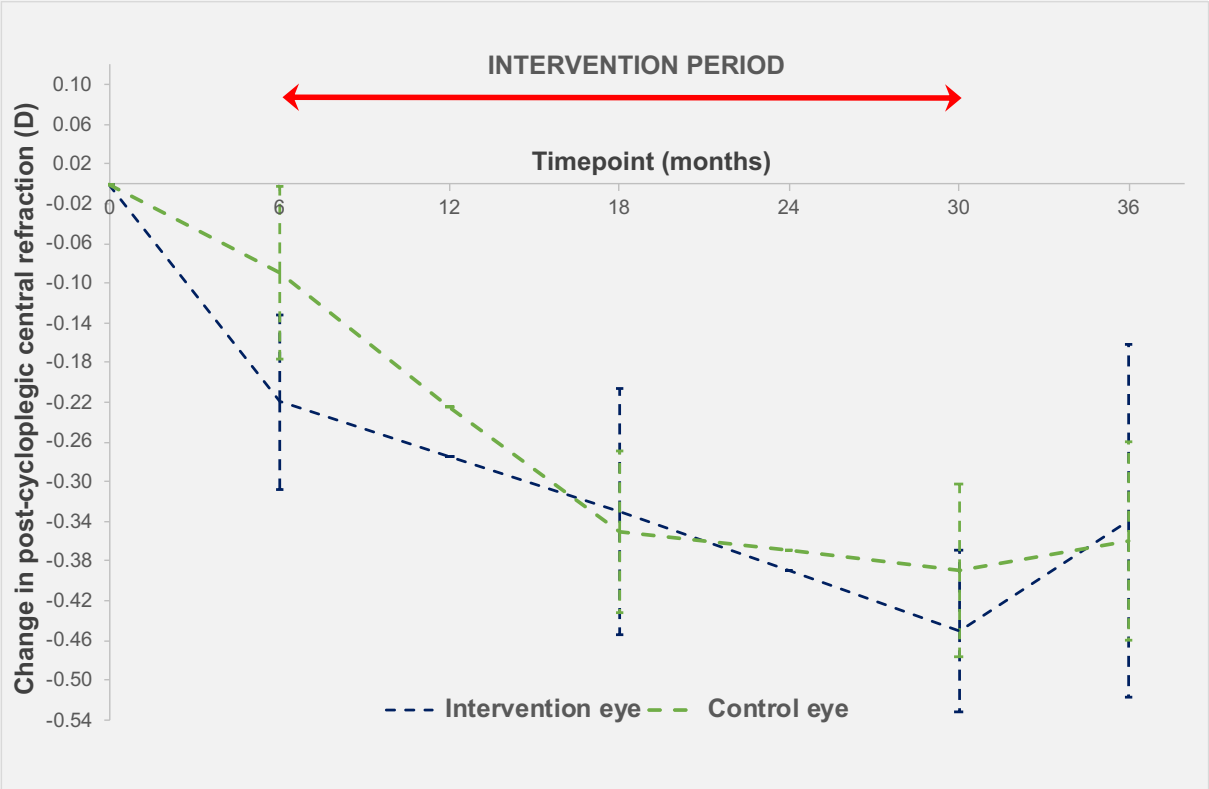

Figure 4.2 Change in MSE post-cycloplegic central refraction (mean ± SEM)

Timepoint (months)	**Refractive error** (D)	
Baseline	+5.28 ± 0.44	+3.37 ± 0.35
6	+5.06 ± 0.46	+3.28 ± 0.37
18	+4.95 ± 0.41	+3.02 ± 0.39
30	+4.83 ± 0.45	+2.98 ± 0.41
36	+4.94 ± 0.56	+3.01 ± 0.44
	Intervention (n = 11)	**Control** (n = 11)

Table 4.4 MSE post-cycloplegic central refractive error at each visit (mean ± SEM). Intervention period shaded red

4.5.2 Secondary outcome measures

4.5.2.1 Unaided DV

Main findings:

- Unaided DV was better for the control eye group than the intervention eye group ($F_{(1, 10)} = 18.730$, $P = 0.001$)
- Unaided DV did not change over time ($F_{(6, 60)} = 1.155$, $P = 0.343$) in either group ($F_{(6, 60)} = 0.615$, $P = 0.717$).

Pairwise comparisons for between-visit analysis (see Figure 4.3 and Table 4.5) showed that for the intervention eye group, unaided DV did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 0.797), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 0.860) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.3 and Table 4.5) showed that for the control eye group, unaided DV did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 0.164), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

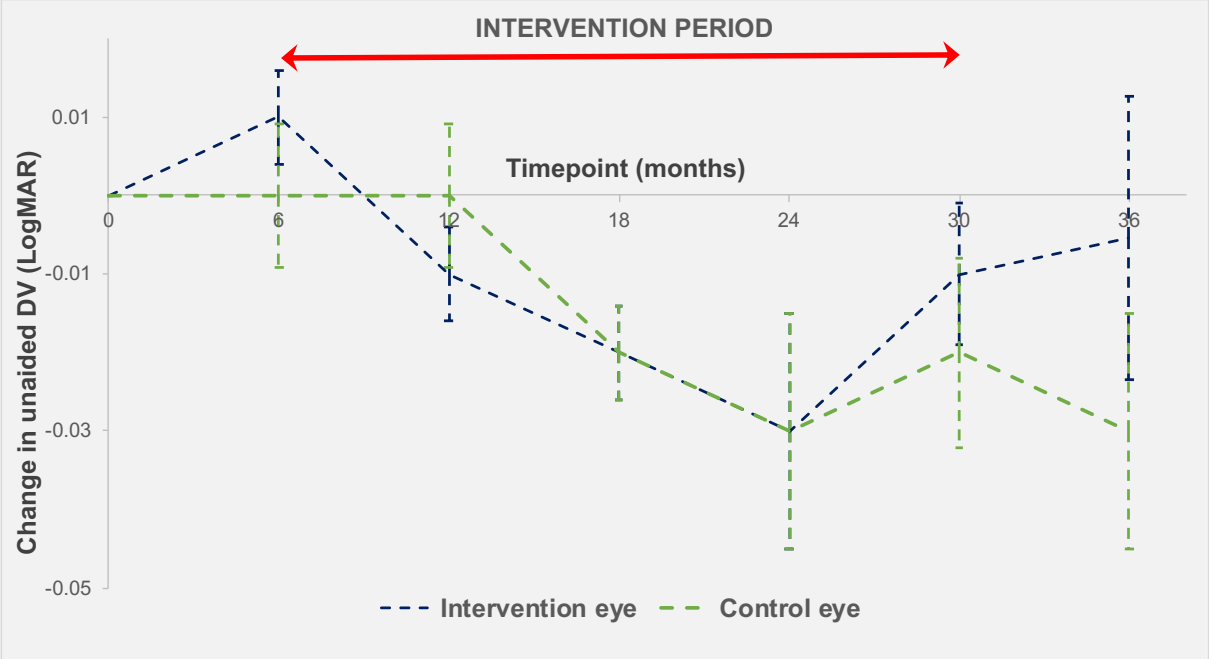

Figure 4.3 Change in unaided DV (mean ± SEM)

Timepoint (months)	**DV** (LogMAR)	
Baseline	0.18 ± 0.04	-0.01 ± 0.02
6	0.19 ± 0.04	-0.02 ± 0.02
12	0.17 ± 0.04	-0.01 ± 0.02
18	0.16 ± 0.04	-0.03 ± 0.02
24	0.15 ± 0.04	-0.04 ± 0.02
30	0.17 ± 0.04	-0.03 ± 0.03
36	0.17 ± 0.05	-0.04 ± 0.03
	Intervention (n = 11)	**Control** (n = 11)

Table 4.5 Unaided DV at 6 m at each visit (mean ± SEM). Intervention period shaded red

4.5.2.2 Spectacle DVA

Main findings:

- Spectacle DVA was better for the control eye group than the intervention eye group ($F_{(1, 10)} = 11.988$, $P = 0.006$) and changed over time ($F_{(6, 60)} = 4.479$, $P = 0.001$) in both groups ($F_{(6, 60)} = 1.437$, $P = 0.216$).

Pairwise comparisons for between-visit analysis (see Figure 4.4 and Table 4.6) showed that for the intervention eye group, spectacle DVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 0.102) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.4 and Table 4.6) showed that for the control eye group, spectacle DVA did not change from baseline to the 6-month timepoint (P = 0.956), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 0.223) and the 30- and 36-month timepoints (P = 1.000).

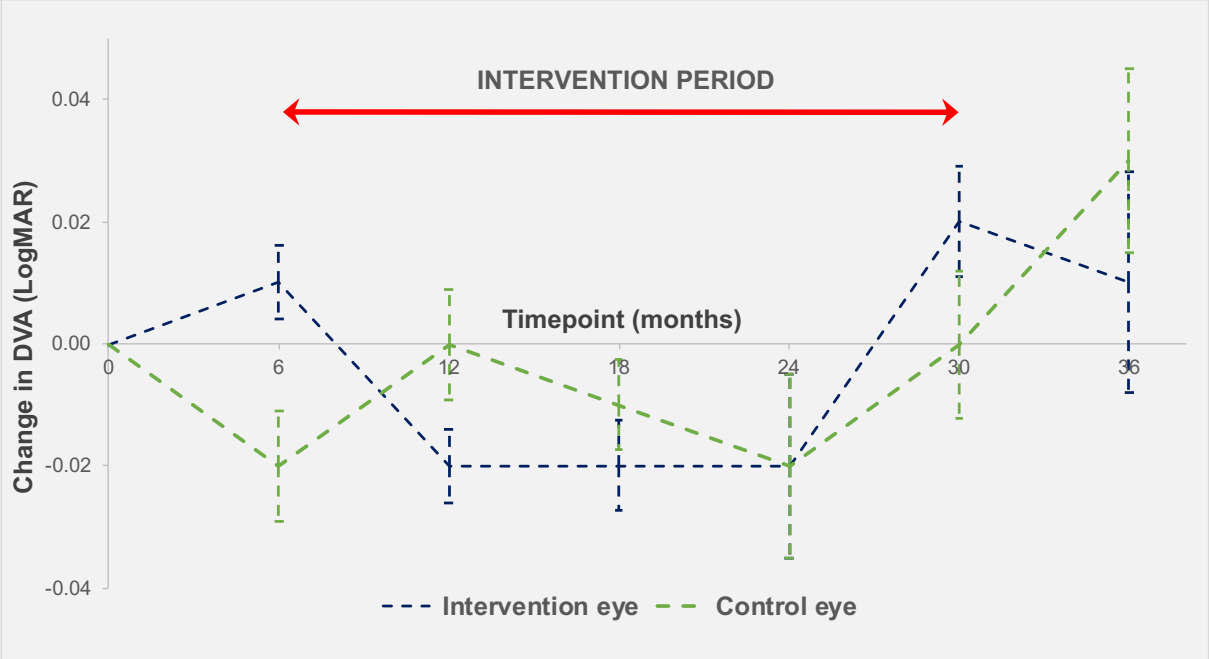

Figure 4.4 Change in spectacle DVA at 6 m (mean ± SEM)

Timepoint (months)	**DVA** (LogMAR)	
Baseline	0.05 ± 0.04	-0.09 ± 0.02
6	0.06 ± 0.04	-0.07 ± 0.01
12	0.03 ± 0.04	-0.09 ± 0.01
18	0.03 ± 0.04	-0.10 ± 0.01
24	0.03 ± 0.04	-0.11 ± 0.01
30	0.07 ± 0.04	-0.09 ± 0.01
36	0.08 ± 0.04	-0.06 ± 0.01
	Intervention (n = 11)	**Control** (n = 11)

Table 4.6 Spectacle DVA at 6 m at each visit (mean ± SEM). Intervention period shaded red

4.5.2.3 CL DVA

Main findings:

- CL DVA was better for the control eye group than the intervention eye group ($F_{(1, 10)}$ = 40.193, P < 0.0005) and improved over time ($F_{(6, 60)}$ = 4.441, P = 0.005) in both groups ($F_{(6, 60)}$ = 2.019, P = 0.110).

Pairwise comparisons for between-visit analysis (see Figure 4.5 and Table 4.7) showed that for the intervention eye group, CL DVA did not change between the 6- and 12-month timepoints (P = 0.075), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000) and the 24- and 30-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.5 and Table 4.7) showed that for the control eye group, CL DVA did not change between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000) and the 24- and 30-month timepoints (P = 1.000).

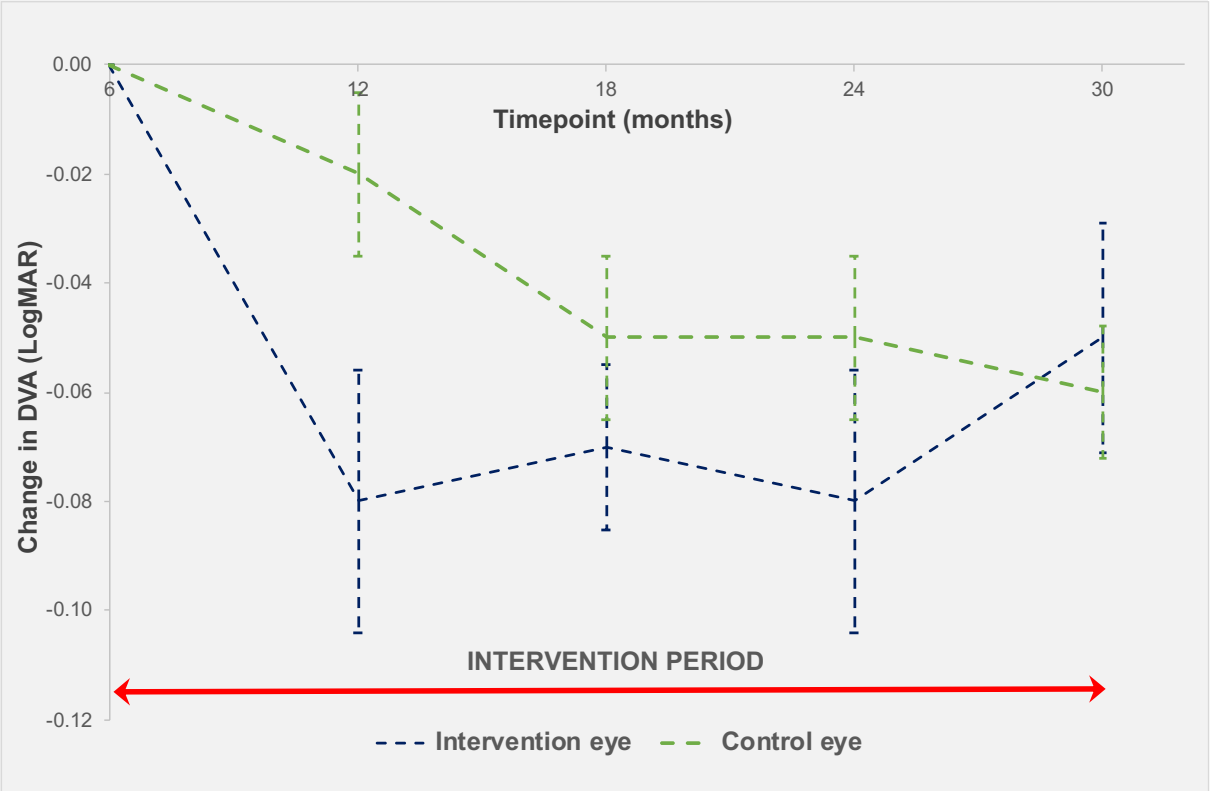

Figure 4.5 Change in CL DVA (mean ± SEM)

Timepoint (months)	**DVA** (LogMAR)	
6	0.24 ± 0.04	0.02 ± 0.02
12	0.16 ± 0.03	0.00 ± 0.02
18	0.17 ± 0.04	-0.03 ± 0.02
24	0.16 ± 0.04	-0.03 ± 0.02
30	0.19 ± 0.04	-0.04 ± 0.02
	Intervention (n = 11)	**Control** (n = 11)

Table 4.7 CL DVA at 6 m at each visit (mean ± SEM). Intervention period shaded red

4.5.2.4 Spectacle DVA *versus* CL DVA

Main findings:

- For the intervention eye group, DVA was better with spectacles than CLs ($F_{(1, 10)}$ = 0.547, P < 0.0005) and changed over time ($F_{(4, 40)}$ = 4.306, P = 0.005) with both forms of correction ($F_{(4, 40)}$ = 2.045, P = 0.106) (see Figure 4.6 and Table 4.8)
- For the control eye group, DVA was better with spectacles than CLs ($F_{(1, 10)}$ = 25.883, P < 0.0005) and changed over time ($F_{(4, 40)}$ = 3.811, P = 0.010) with both forms of correction ($F_{(4, 40)}$ = 2.576, P = 0.052) (see Figure 4.7 and Table 4.9).

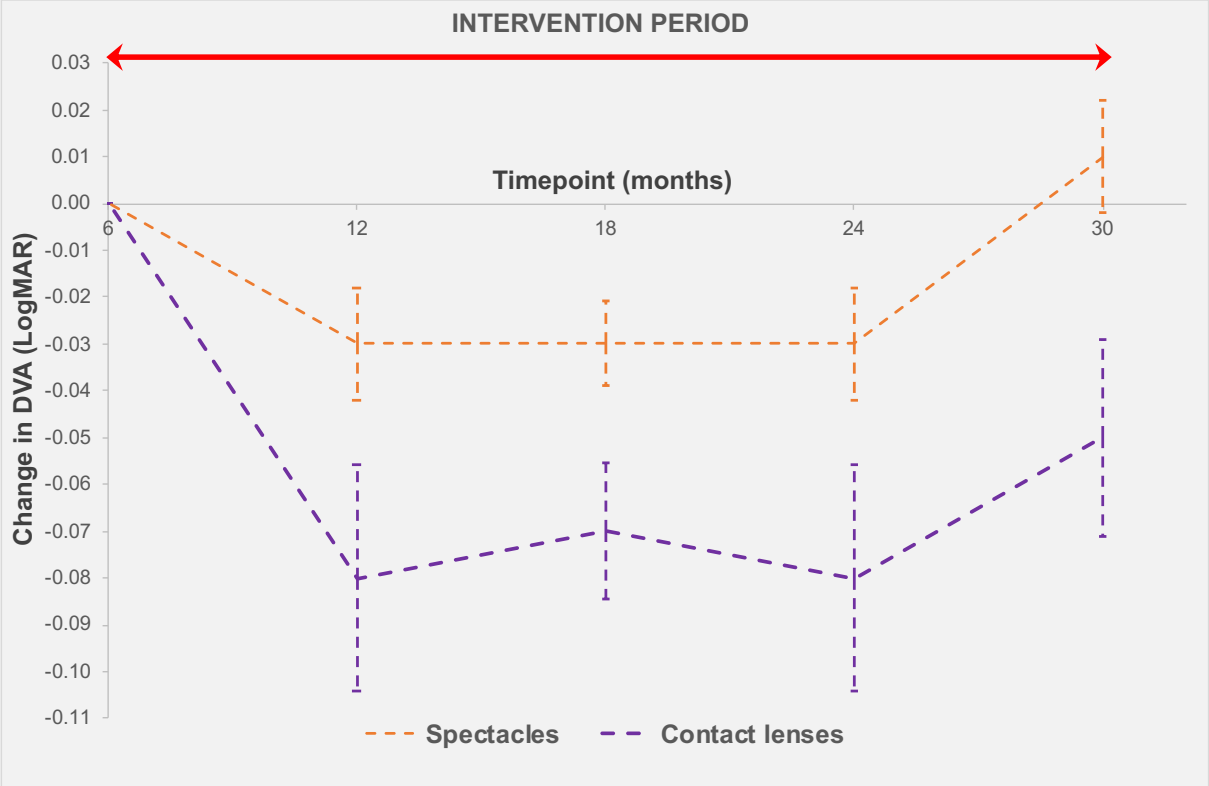

Figure 4.6 Change in spectacle DVA *versus* CL DVA at 6 m for the intervention eye group (mean ± SEM). Measures at the first timepoint taken at the first CL aftercare visit

Timepoint (months)	**DVA** (LogMAR)	
6	0.06 ± 0.04	0.24 ± 0.04
12	0.03 ± 0.04	0.16 ± 0.03
18	0.03 ± 0.04	0.17 ± 0.04
24	0.03 ± 0.04	0.16 ± 0.04
30	0.07 ± 0.04	0.19 ± 0.04
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.8 Spectacle DVA *versus* CL DVA at 6 m for the intervention eye group (mean ± SEM). Measures at the first timepoint taken at the first CL aftercare visit

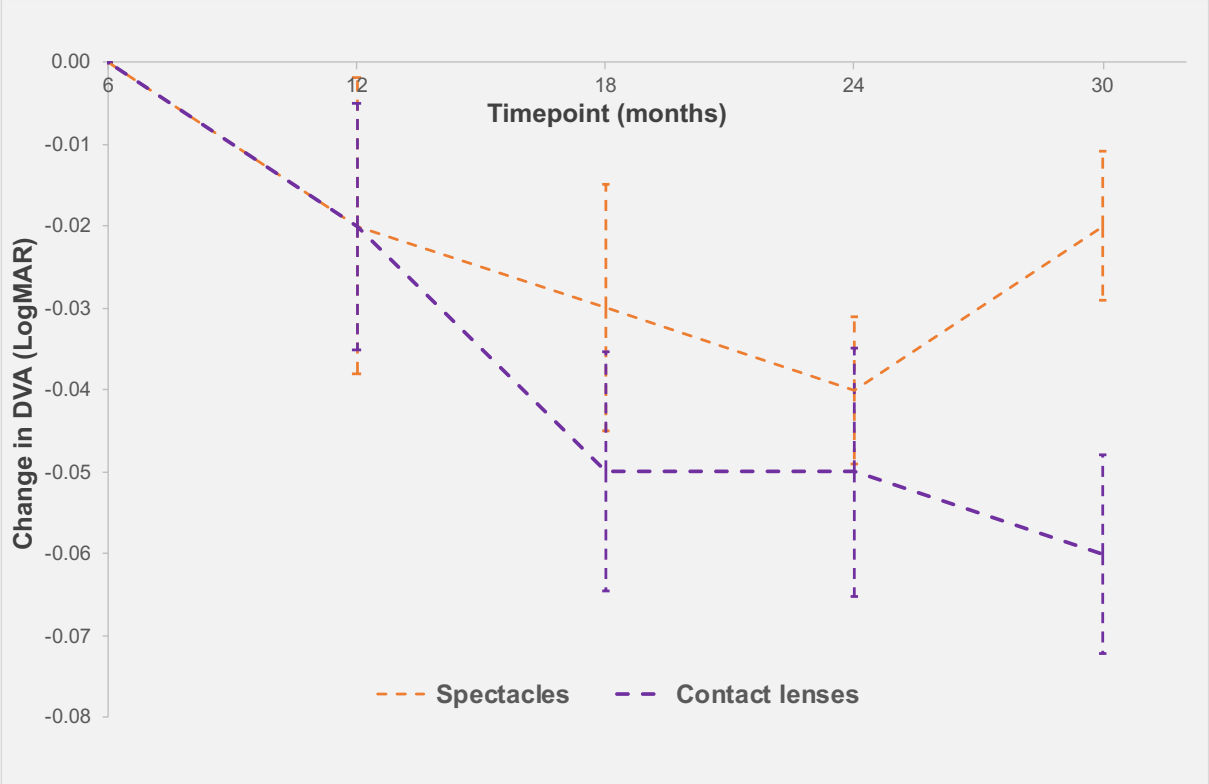

Figure 4.7 Change in spectacle DVA *versus* CL DVA at 6 m for the control eye group (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

Timepoint (months)	**DVA** (LogMAR)	
6	-0.07 ± 0.01	0.02 ± 0.02
12	-0.09 ± 0.01	0.00 ± 0.02
18	-0.10 ± 0.01	-0.03 ± 0.02
24	-0.11 ± 0.01	-0.03 ± 0.02
30	-0.09 ± 0.01	-0.04 ± 0.02
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.9 Spectacle DVA *versus* CL DVA at 6 m for the control eye group (mean ± SEM). Measures at the first timepoint taken at the first CL aftercare visit

4.5.2.5 Spectacle NVA

Main findings:

- Spectacle NVA was better for the control eye group than the intervention eye group ($F_{(1, 10)} = 26.532$, $P < 0.0005$) and improved over time ($F_{(6, 60)} = 9.838$, $P < 0.0005$) in both groups ($F_{(6, 60)} = 1.643$, $P = 0.151$).

Pairwise comparisons for between-visit analysis (see Figure 4.8 and Table 4.10) showed that for the intervention eye group, spectacle NVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 0.797), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.8 and Table 4.10) showed that for the control eye group, spectacle NVA did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000) or the 12- and 18-month timepoints (P = 1.000). Spectacle NVA improved between the 18- and 24-month timepoints (P

= 0.039) but did not change between the 24- and 30-month timepoints (P = 1.000) nor the 30- and 36-month timepoints (P = 1.000).

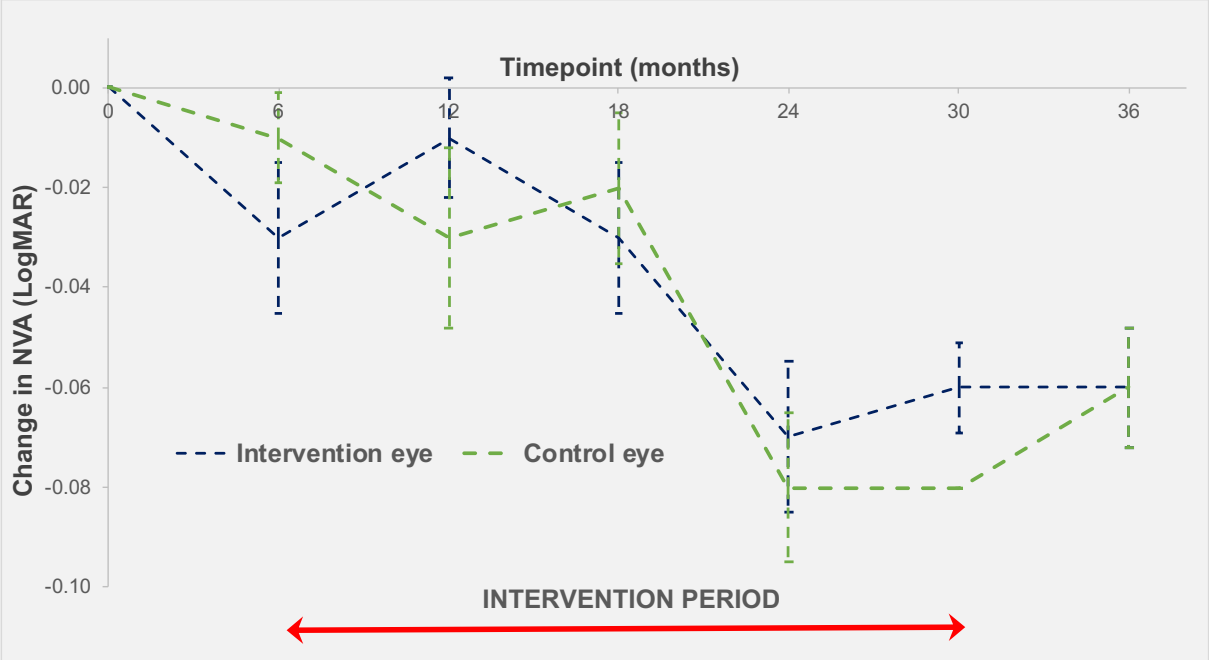

Figure 4.8 Change in spectacle NVA at 0.25 m (mean ± SEM)

Timepoint (months)	**NVA** (LogMAR)	
Baseline	0.28 ± 0.02	0.19 ± 0.02
6	0.25 ± 0.02	0.18 ± 0.01
12	0.27 ± 0.02	0.16 ± 0.02
18	0.25 ± 0.02	0.17 ± 0.01
24	0.21 ± 0.02	0.11 ± 0.02
30	0.22 ± 0.02	0.11 ± 0.02
36	0.22 ± 0.02	0.13 ± 0.02
	Intervention (n = 11)	**Control** (n = 11)

Table 4.10 Spectacle NVA at 0.25 m at each visit (mean ± SEM). Intervention period shaded red

4.5.2.6 CL NVA

Main findings:

- CL NVA was better for the control eye group than the intervention eye group ($F_{(1, 10)}$ = 45.000, P < 0.0005) and improved over time ($F_{(6, 60)}$ = 6.378, P < 0.0005) in both groups ($F_{(6, 60)}$ = 1.034, P = 0.401).

Pairwise comparisons for between-visit analysis (see Figure 4.9 and Table 4.11) showed that for the intervention eye group, CL NVA did not change between the 6- and 12-month timepoints (P = 0.959), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000) and the 24- and 30-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.9 and Table 4.11) showed that for the control eye group, CL NVA did not change between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 0.816) and the 24- and 30-month timepoints (P = 1.000).

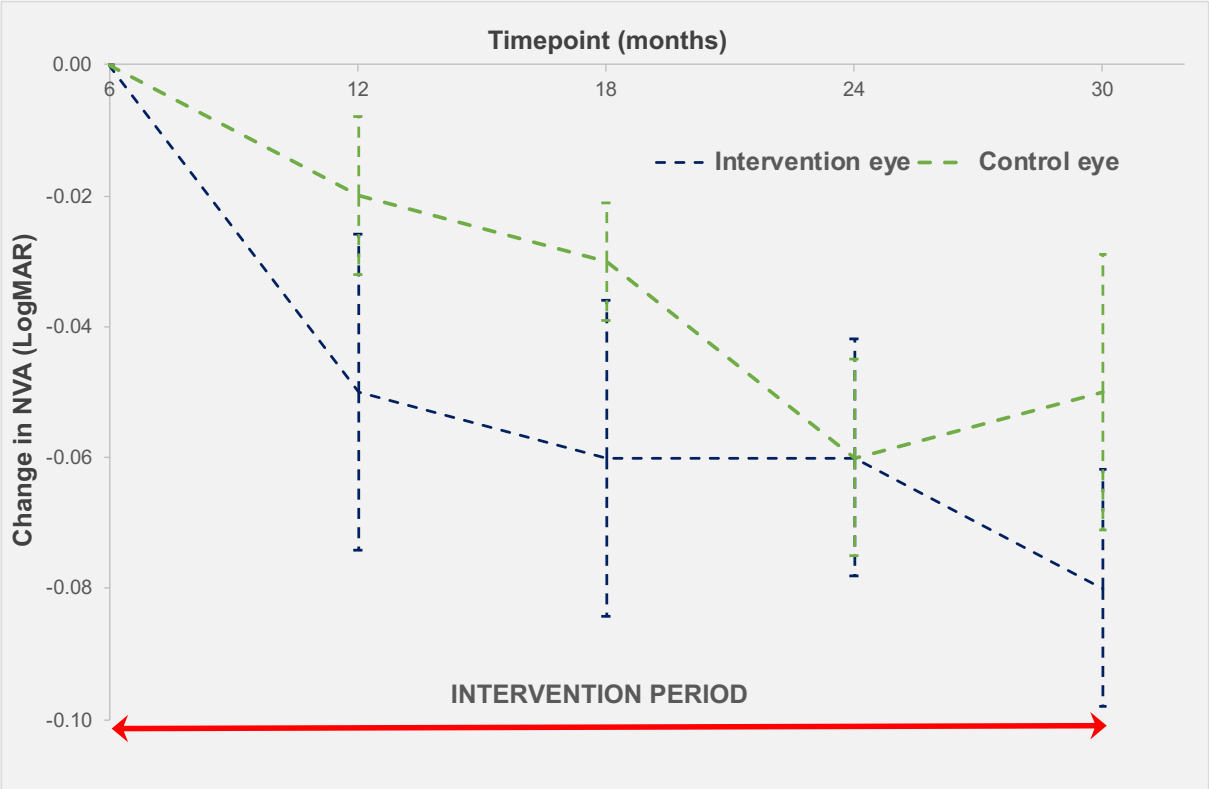

Figure 4.9 Change in CL NVA at 0.25 m (mean ± SEM)

Timepoint (months)	**NVA** (LogMAR)	
6	0.30 ± 0.02	0.22 ± 0.01
12	0.25 ± 0.02	0.20 ± 0.00
18	0.24 ± 0.02	0.19 ± 0.01
24	0.24 ± 0.02	0.16 ± 0.02
30	0.22 ± 0.01	0.17 ± 0.01
	Intervention (n = 11)	**Control** (n = 11)

Table 4.11 CL NVA at 0.25 m at each visit (mean ± SEM). Intervention period shaded red

4.5.2.7 Spectacle NVA *versus* CL NVA

Main findings:

- For the intervention eye group, NVA was similar with spectacles and CLs ($F_{(1, 10)}$ = 0.558, P = 0.472) and improved over time ($F_{(4, 40)}$ = 5.523, P = 0.001) with CL correction only ($F_{(4, 40)}$ = 3.320, P = 0.019) (see Figure 4.10 and Table 4.12)
- For the control eye group, NVA was better with spectacles than CLs ($F_{(1, 10)}$ = 17.872, P = 0.002) and improved over time ($F_{(4, 40)}$ = 9.744, P < 0.0005) with both forms of correction ($F_{(4, 40)}$ = 2.088, P = 0.100) (see Figure 4.11 and Table 4.13).

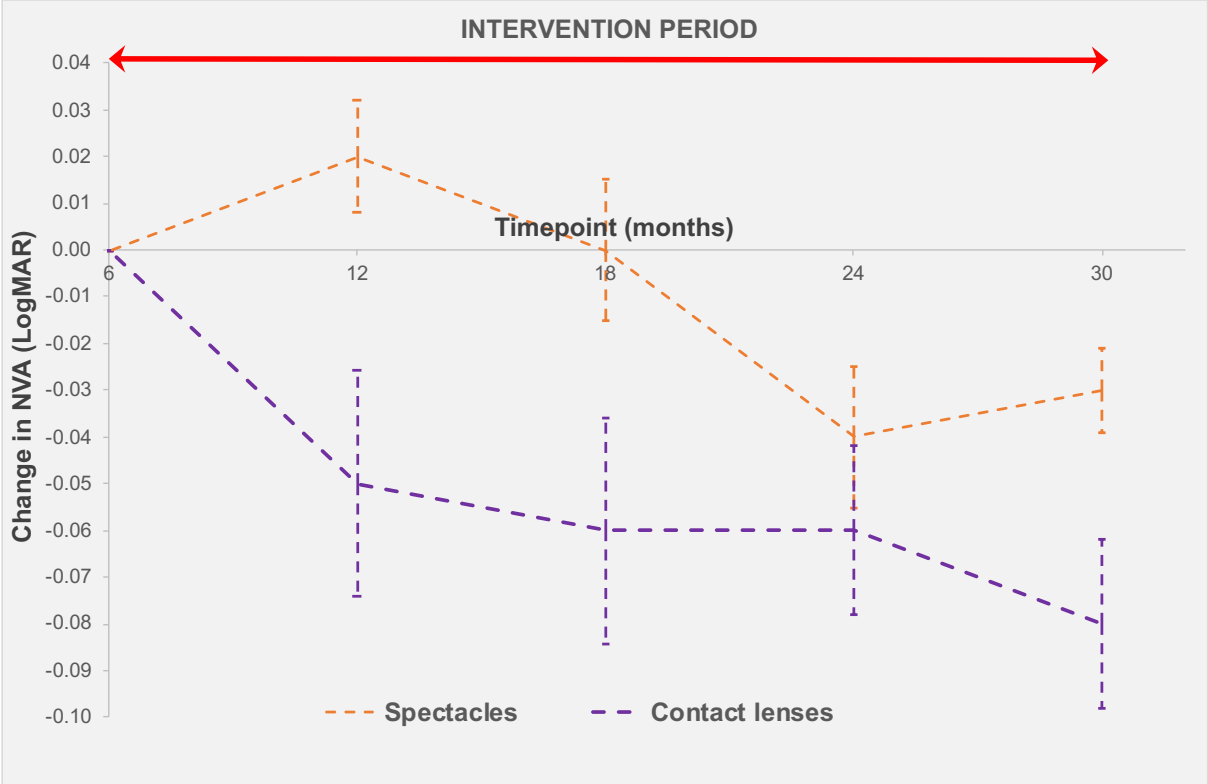

Figure 4.10 Change in spectacle NVA *versus* CL NVA at 0.25 m for the intervention eye group (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

Timepoint (months)	**NVA** (LogMAR)	
6	0.25 ± 0.02	0.30 ± 0.02
12	0.27 ± 0.02	0.25 ± 0.02
18	0.25 ± 0.02	0.24 ± 0.02
24	0.21 ± 0.02	0.24 ± 0.02
30	0.22 ± 0.02	0.22 ± 0.01
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.12 Spectacle NVA *versus* CL NVA at 0.25 m for the intervention eye group (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

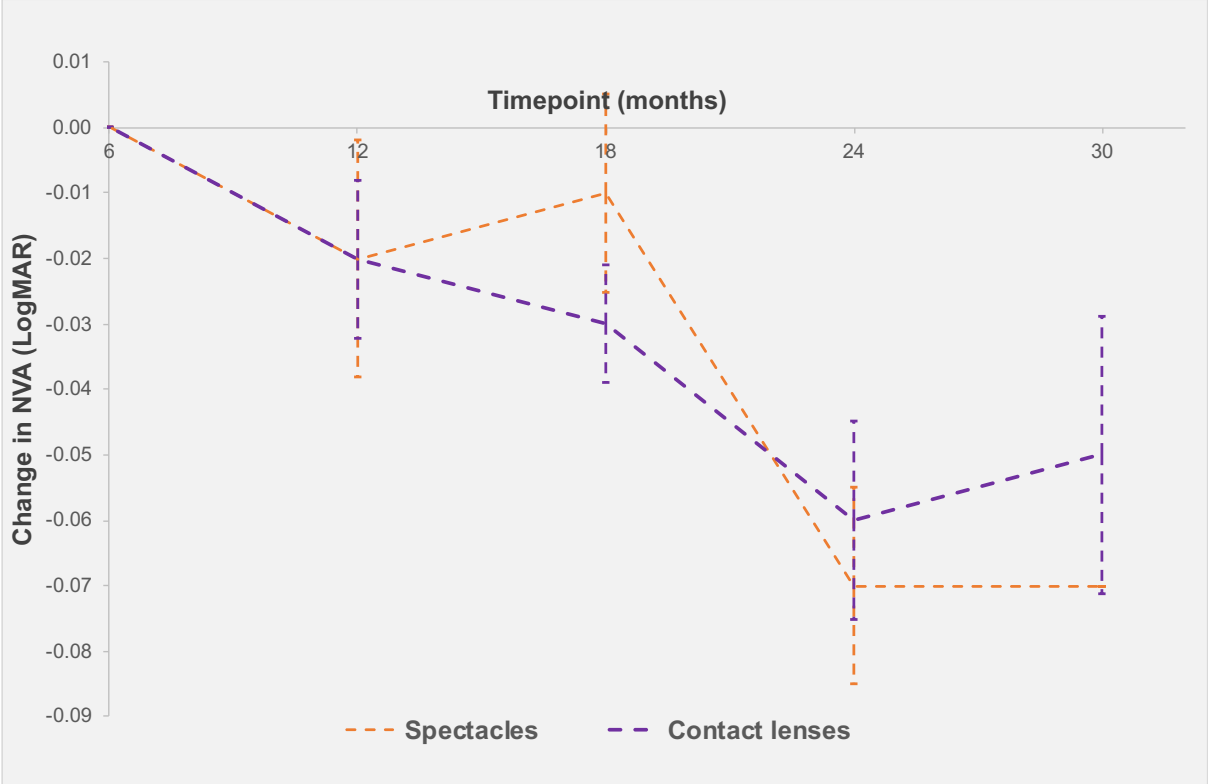

Figure 4.11 Change in spectacle NVA *versus* CL NVA at 0.25 m for the control eye group (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

Timepoint (months)	**NVA** (LogMAR)	
6	0.18 ± 0.01	0.22 ± 0.01
12	0.16 ± 0.02	0.20 ± 0.00
18	0.17 ± 0.01	0.19 ± 0.01
24	0.11 ± 0.02	0.16 ± 0.02
30	0.11 ± 0.02	0.17 ± 0.01
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.13 Spectacle NVA *versus* CL NVA at 0.25 m for the control eye group (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

4.5.2.8 Stereoacuity with spectacle correction

Main findings:

- Stereoacuity did not change over time ($F_{(6, 54)} = 1.070$, $P = 0.392$).

Pairwise comparisons for between-visit analysis (see Figure 4.12 and Table 4.14) showed that stereoacuity did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

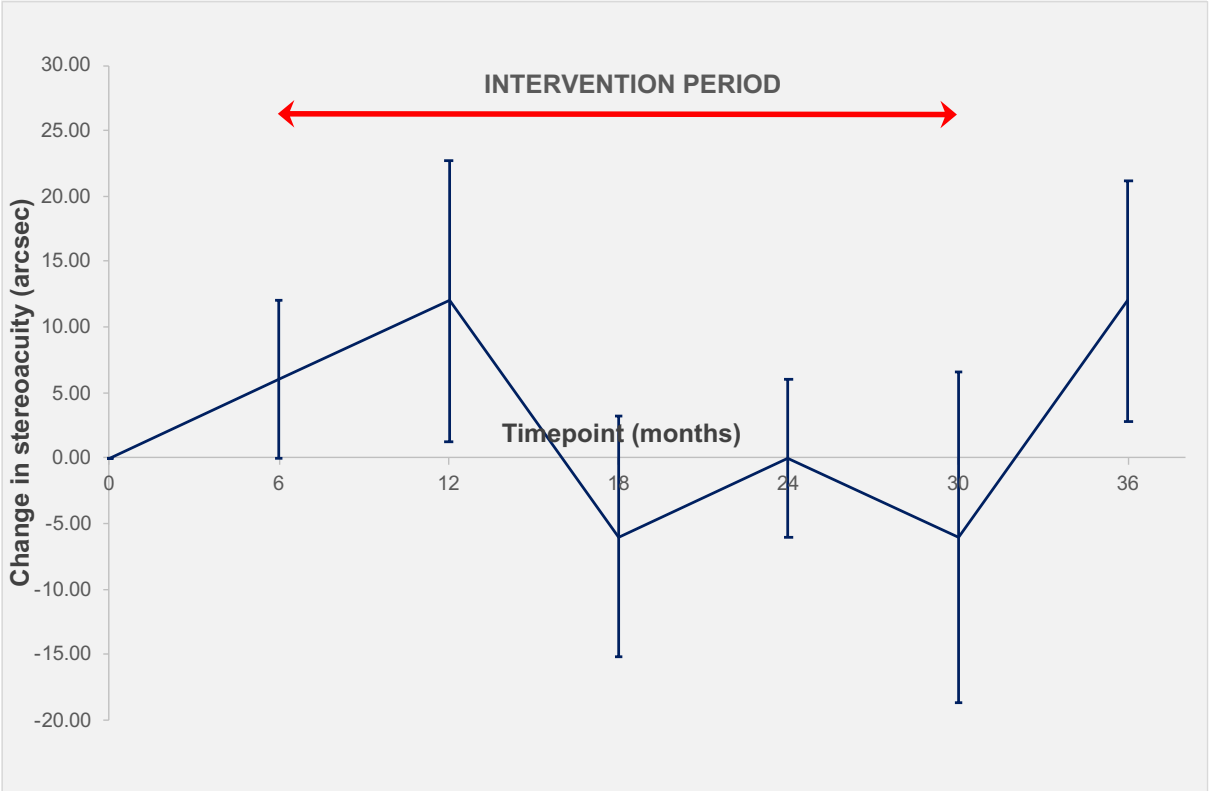

Figure 4.12 Change in stereoacuity with spectacle correction (mean ± SEM). Excludes 1 participant who was unable to complete the grading plates

Timepoint (months)	**Stereoacuity** (arcsec)
Baseline	78.00 ± 9.17
6	84.00 ± 9.80
12	90.00 ± 10.00
18	72.00 ± 8.00
24	78.00 ± 9.17
30	72.00 ± 8.00
36	90.00 ± 10.00
	(n = 10)

Table 4.14 Stereoacuity at each visit (mean ± SEM). Intervention period shaded red. Excludes participants that were unable to complete the grading plates

4.5.2.9 Stereoacuity: spectacle correction *versus* CL correction

Main findings:

- Stereoacuity was similar with spectacles and CLs ($F_{(1, 9)} = 4.338$, $P = 0.067$) and did not change over time ($F_{(1, 9)} = 3.524$, $P = 0.093$) with either form of correction ($F_{(1, 9)} = 3.128$, $P = 0.111$).

Pairwise comparisons for between-visit analysis (see Table 4.15) showed that with spectacle correction, stereoacuity was similar at the 12- and 24-month timepoints ($P = 0.168$).

Pairwise comparisons for between-visit analysis (see Table 4.15) showed that with CL correction, stereoacuity was similar at the 12- and 24-month timepoints ($P = 0.095$).

Timepoint (months)	**Stereoacuity** (arcsec)	
12	90.00 ± 10.00	168.00 ± 39.80
24	78.00 ± 9.17	114.00 ± 16.61
	Spectacles (n = 10)	**CLs** (n = 10)

Table 4.15 Stereoacuity with spectacle correction *versus* CL correction (mean ± SEM). Intervention period shaded red. Excludes participants that were unable to complete the grading plates

4.5.2.10 Cover test with spectacle correction

A summary of binocular status with spectacle correction at distance and near for the participants is detailed in Table 4.16.

	Cover test	
Participant	**Distance at 6 m**	**Near at 0.25 m**
1	Orthophoria	Orthophoria
2	Orthophoria	Orthophoria
3	Orthophoria	Small exophoria
4	Orthophoria	Orthophoria
5	Orthophoria	Orthophoria
6	Orthophoria	Orthophoria
7	Orthophoria	Orthophoria
8	Orthophoria	Orthophoria
9	Orthophoria	Orthophoria
10	Orthophoria	Orthophoria
11	Orthophoria	Orthophoria

Table 4.16 Cover test with spectacle correction at distance and near for the intervention group

4.5.2.11 CS with spectacle correction

Main findings:

- CS with spectacle correction was better in the control eye group than the intervention eye group ($F_{(1, 10)} = 9.146$, $P = 0.013$) and did not change over time ($F_{(2, 20)} = 0.510$, $P = 0.608$) in either group ($F_{(2, 20)} = 0.377$, $P = 0.690$).

Pairwise comparisons for between-visit analysis (see Figure 4.13 and Table 4.17) showed that for the intervention eye group, CS with spectacle correction did not change between the 6- and 30-month timepoints ($P = 1.000$), nor between the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 4.13 and Table 4.17) showed that for the control eye group, CS with spectacle correction did not change between the 6- and 30-month timepoints (P = 0.501), nor between the 30- and 36-month timepoints (P = 1.000).

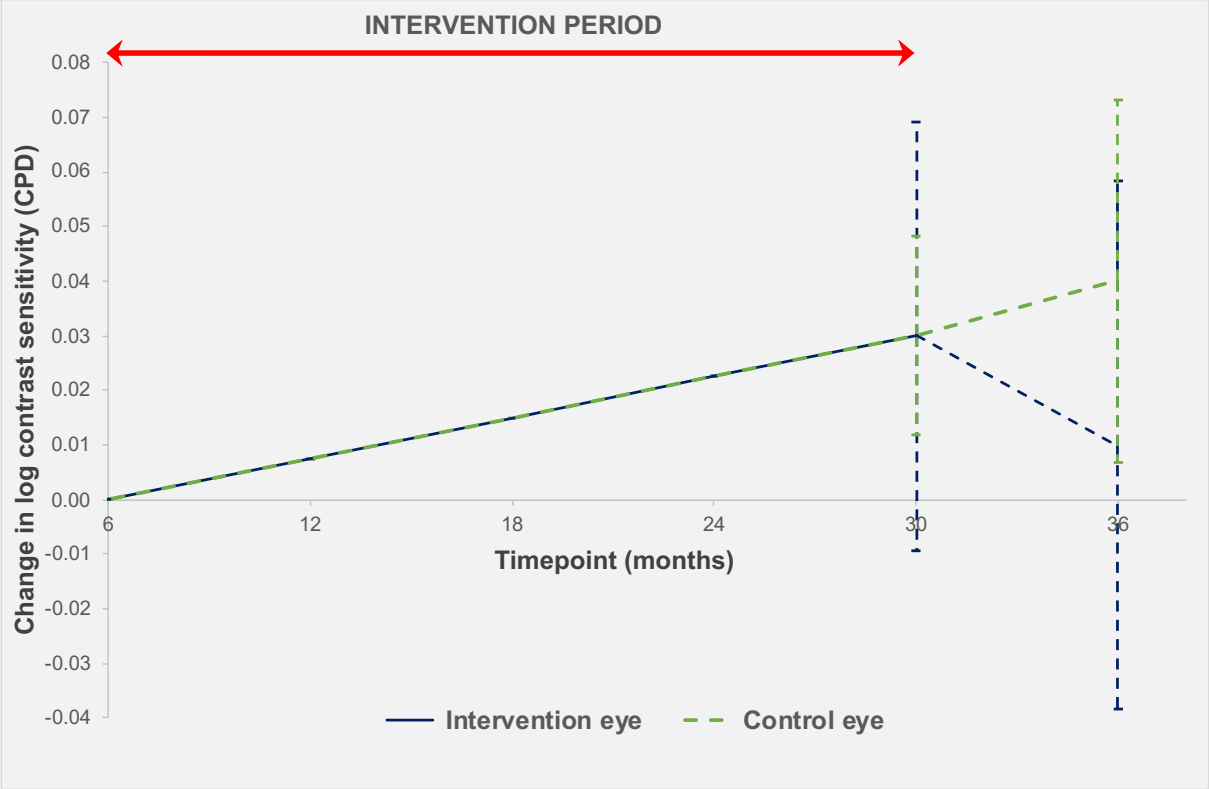

Figure 4.13 Change in CS with spectacle correction at 1 m (mean ± SEM)

Timepoint (months)	**Log CS** (CPD)	
6	1.51 ± 0.02	1.58 ± 0.02
30	1.54 ± 0.03	1.61 ± 0.02
36	1.53 ± 0.04	1.62 ± 0.03
	Intervention (n = 11)	**Control** (n = 11)

Table 4.17 CS with spectacle correction at 1 m. Intervention period shaded red

4.5.2.12 CS with CL correction

Main findings:

- CS with CL correction was better for the control eye group than the intervention eye group ($F_{(1, 10)} = 5.213$, $P = 0.046$) and did not change over time ($F_{(1, 10)} = 0.290$, $P = 0.602$) in either group ($F_{(1, 10)} = 3.378$, $P = 0.096$).

Pairwise comparisons for between-visit analysis (see Table 4.18) showed that for the intervention eye group, CS with CL correction did not change between the 6- and 30-month timepoints ($P = 0.796$).

Pairwise comparisons for between-visit analysis (see Table 4.18) showed that for the control eye group, CS with CL correction did not change between the 6- and 30-month timepoints ($P = 0.104$).

Timepoint (months)	**Log CS** (CPD)	
6	1.53 ± 0.02	1.54 ± 0.02
30	1.51 ± 0.03	1.60 ± 0.02
	Intervention (n = 11)	**Control** (n = 11)

Table 4.18 CS with CL correction at 1 m. Intervention period shaded red

4.5.2.13 CS: spectacle correction *versus* CL correction

Main findings:

- For the intervention eye group, mean CS was similar with spectacle correction and CL correction ($F_{(1, 10)} = 0.102$, $P = 0.756$) and did not change over time ($F_{(1, 10)} = 0.036$, $P = 0.852$) with either form of correction ($F_{(1, 10)} = 0.506$, $P = 0.493$) (see Table 4.19)
- For the control eye group, mean CS was similar with spectacle correction and CL correction ($F_{(1, 10)} = 2.222$, $P = 0.167$) and did not change over time ($F_{(1, 10)} = 3.750$, $P = 0.082$) with either form of correction ($F_{(1, 10)} = 1.000$, $P = 0.341$) (see Table 4.20).

Timepoint (months)	**Log CS** (CPD)	
6	1.51 ± 0.02	1.53 ± 0.03
30	1.54 ± 0.03	1.51 ± 0.03
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.19 CS with spectacle correction *versus* CL correction at 1 m for the intervention eye group (mean ± SEM). Intervention period shaded red. Measures at the initial timepoint taken at the first CL aftercare visit

Timepoint (months)	**Log CS** (CPD)	
6	1.58 ± 0.02	1.54 ± 0.02
30	1.61 ± 0.02	1.60 ± 0.02
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.20 CS with spectacle correction *versus* CL correction at 1 m for the control eye group (mean ± SEM). Intervention period shaded red. Measures at the initial timepoint taken at the first CL aftercare visit

4.5.2.14 CC

Main findings:

- CC was similar for the intervention eye group and control eye group ($F_{(1, 10)} = 0.143$, $P = 0.713$) and did not change over time ($F_{(6, 60)} = 1.704$, $P = 0.136$) in either group ($F_{(6, 120)} = 0.767$, $P = 0.599$).

Pairwise comparisons for between-visit analysis (see Figure 4.14 and Table 4.21) showed that for the intervention eye group, CC did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 0.222), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.14 and Table 4.21) showed that for the control eye group, CC did not change from baseline to the 6-month timepoint (P = 0.950), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

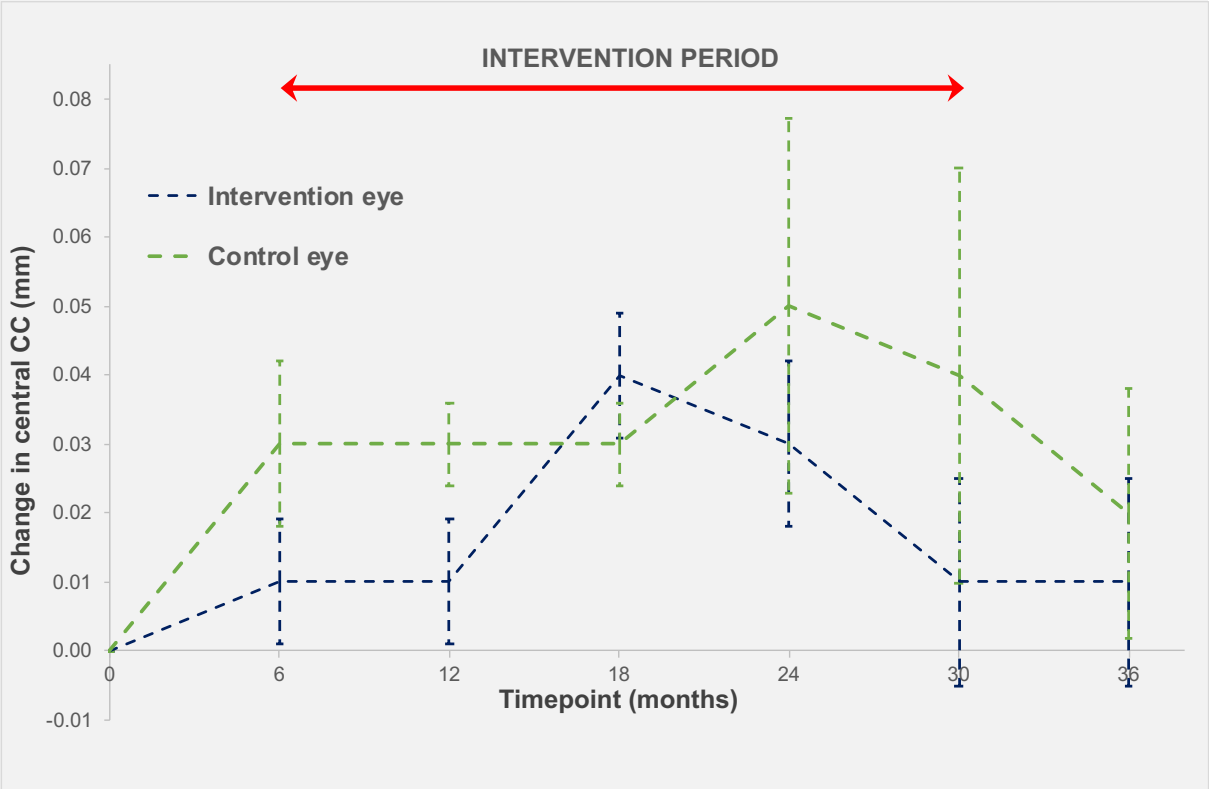

Figure 4.14 Change in CC (mean ± SEM)

Timepoint (months)	**CC** (mm)	
Baseline	7.78 ± 0.10	7.76 ± 0.09
6	7.79 ± 0.09	7.79 ± 0.09
12	7.79 ± 0.10	7.79 ± 0.09
18	7.82 ± 0.09	7.79 ± 0.08
24	7.81 ± 0.10	7.81 ± 0.09
30	7.79 ± 0.10	7.80 ± 0.08
36	7.79 ± 0.09	7.78 ± 0.09
	Intervention (n = 11)	**Control** (n = 11)

Table 4.21 CC at each visit (mean ± SEM). Intervention period shaded red

4.5.2.15 ACD

Main findings:

- ACD was greater for the control eye group than intervention eye group ($F_{(1, 10)} = 8.401$, $P = 0.016$) and did not change over time ($F_{(4, 40)} = 1.436$, $P = 0.240$) in either group ($F_{(4, 40)} = 0.487$, $P = 0.745$).

Pairwise comparisons for between-visit analysis (see Figure 4.15 and Table 4.22) showed that for the intervention eye group, ACD did not change from baseline to the 6-month timepoint ($P = 0.212$), nor between the 6- and 18-month timepoints ($P = 0.066$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

Pairwise comparisons for between-visit analysis (see Figure 4.15 and Table 4.22) showed that for the control eye group, ACD did not change from baseline to the 6-month timepoint ($P = 0.063$), nor between the 6- and 18-month timepoints ($P = 1.000$), 18- and 30-month timepoints ($P = 1.000$) and the 30- and 36-month timepoints ($P = 1.000$).

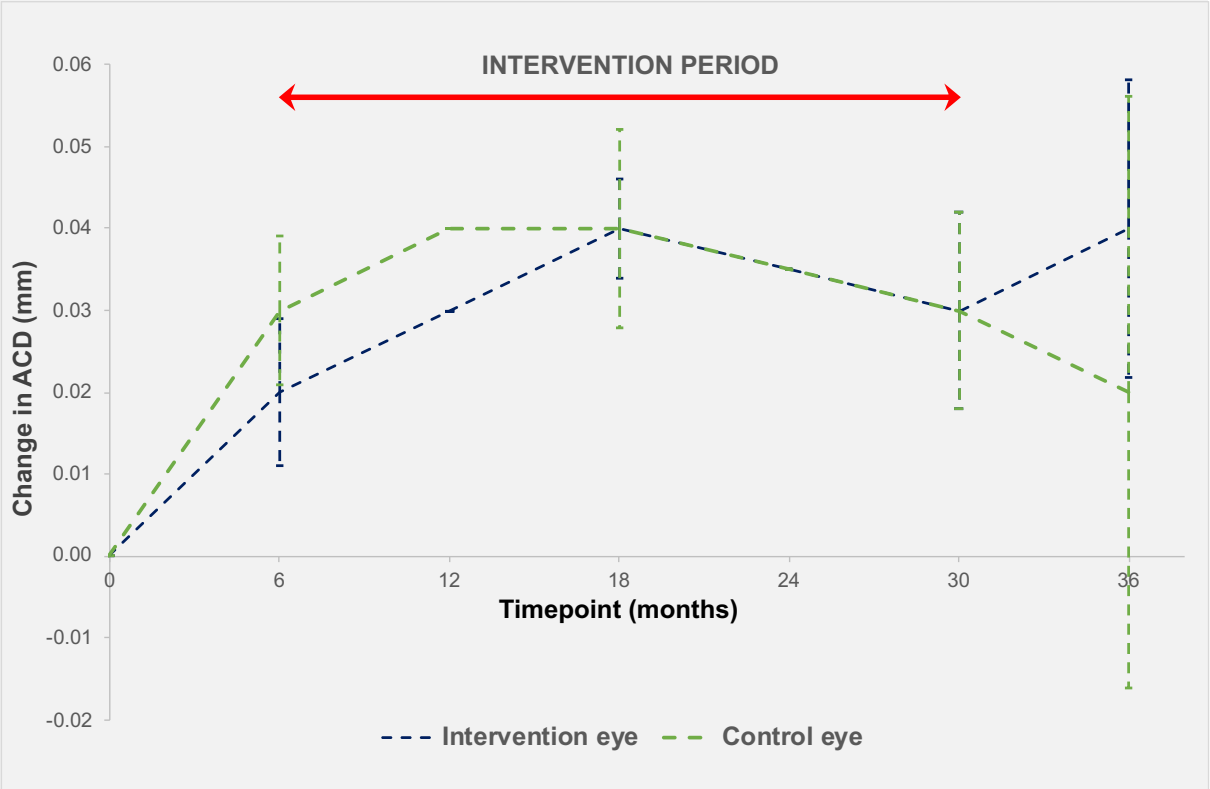

Figure 4.15 Change in ACD (mean ± SEM)

Timepoint (months)	**ACD** (mm)	
Baseline	3.33 ± 0.09	3.45 ± 0.08
6	3.35 ± 0.09	3.48 ± 0.08
18	3.37 ± 0.09	3.49 ± 0.08
30	3.36 ± 0.09	3.48 ± 0.08
36	3.37 ± 0.09	3.47 ± 0.08
	Intervention (n = 11)	**Control** (n = 11)

Table 4.22 ACD at each visit (mean ± SEM). Intervention period shaded red

4.5.2.16 Pupil size

Main findings:

- Pupil size was similar for the intervention eye group and control eye group ($F_{(1, 10)}$ = 1.432, P = 0.259)
- Pupil size was smaller in photopic conditions than in mesopic conditions ($F_{(1, 10)}$ = 55.694, P < 0.0005) in both groups ($F_{(1, 10)}$ = 0.226, P = 0.645) (see Figure 4.16 and Table 4.23).

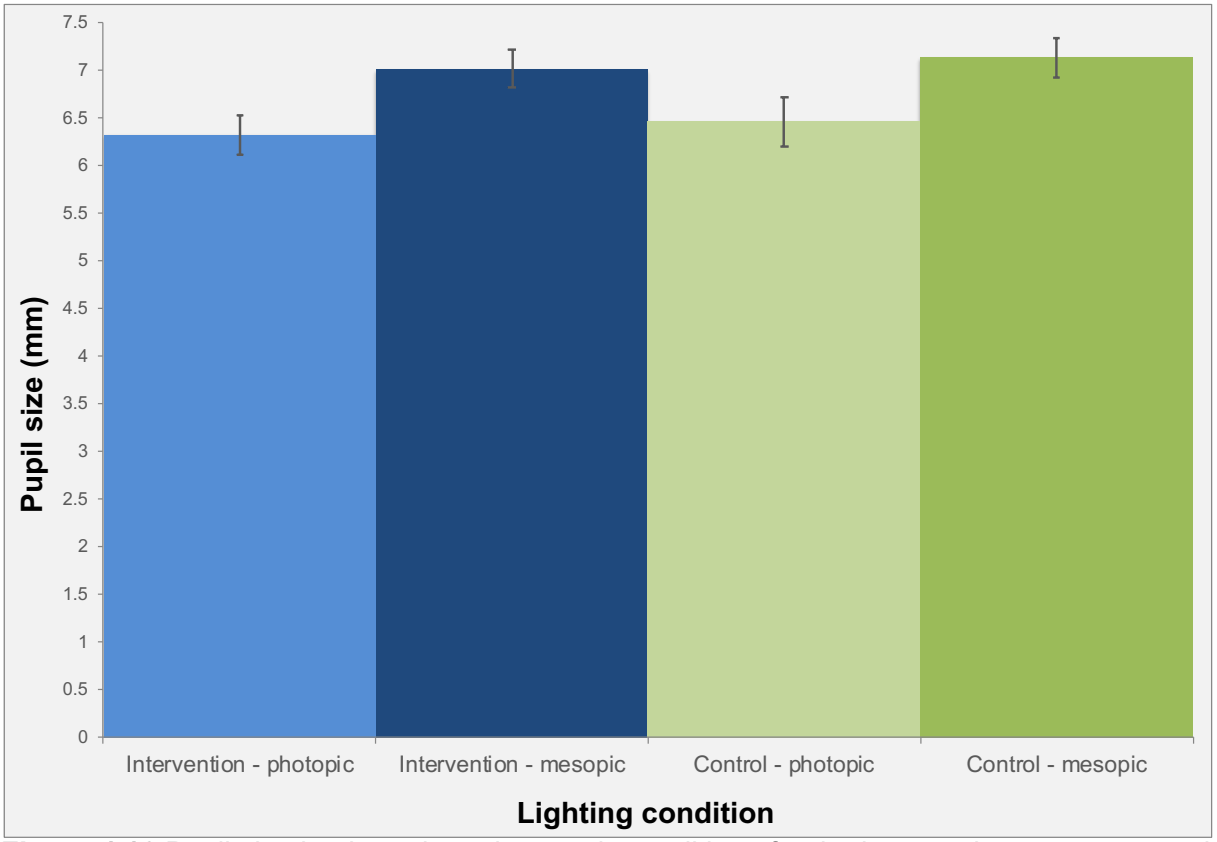

Figure 4.16 Pupil size in photopic and mesopic conditions for the intervention eye group and control eye group with CL *in situ* (mean ± SEM)

	Pupil size (mm)			
Timepoint (months)	Intervention - photopic	Control - photopic	Intervention - mesopic	Control - mesopic
12	6.31 ± 0.21	6.45 ± 0.26	7.01 ± 0.20	7.12 ± 0.21

Table 4.23 Pupil size in photopic and mesopic conditions for the intervention eye group and control eye group with CL *in situ* (mean ± SEM)

4.5.2.17 Amplitude of accommodation

Main findings:

- Amplitude of accommodation was similar for the intervention eye and control eye groups ($F_{(1, 10)} = 3.778$, $P = 0.081$) and did not change over time ($F_{(6, 60)} = 0.404$, $P = 0.873$) in either group ($F_{(6, 60)} = 2.157$, $P = 0.060$).

Pairwise comparisons for between-visit analysis (see Figure 4.17 and Table 4.24) showed that for the intervention eye group, amplitude of accommodation did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.17 and Table 4.24) showed that for the control eye group, amplitude of accommodation did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

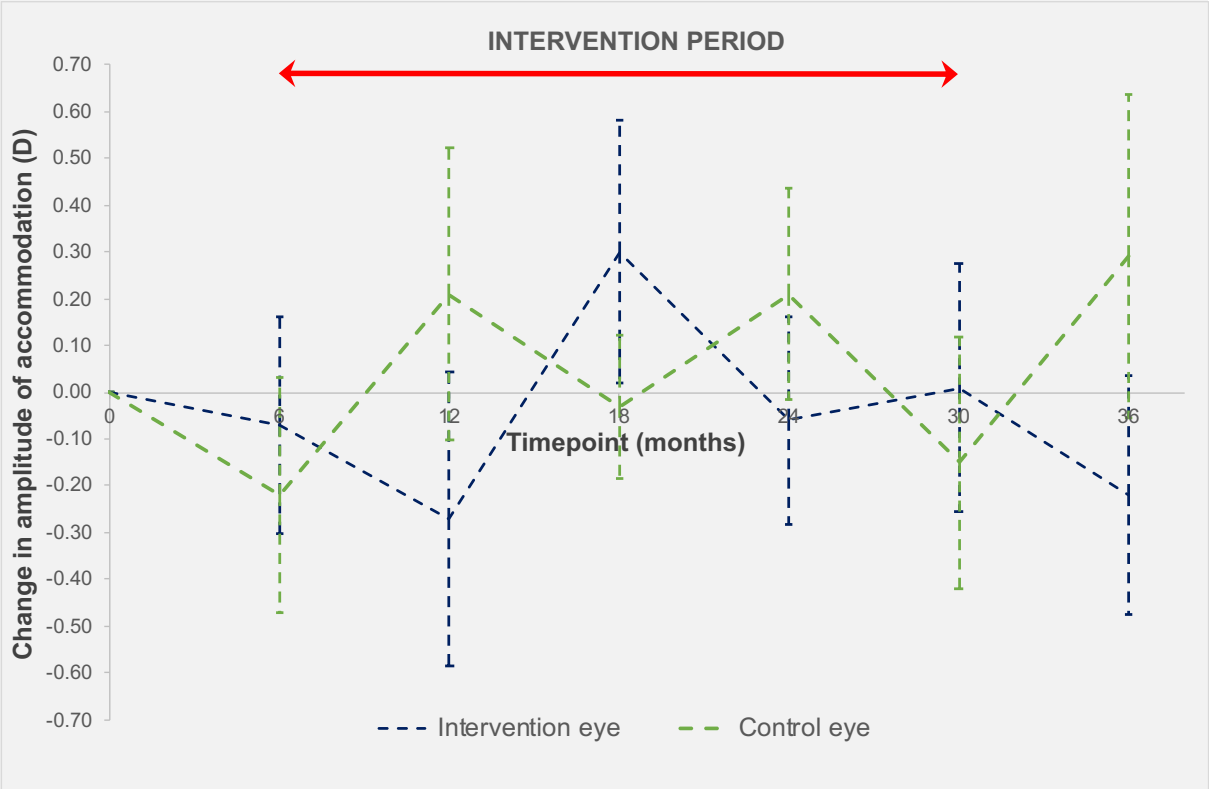

Figure 4.17 Change in amplitude of accommodation (mean ± SEM)

Timepoint (months)	**Amplitude of accommodation** (D)	
Baseline	11.01 ± 0.48	11.33 ± 0.38
6	10.94 ± 0.37	11.11 ± 0.37
12	10.74 ± 0.40	11.54 ± 0.26
18	11.31 ± 0.50	11.30 ± 0.29
24	10.95 ± 0.46	11.54 ± 0.38
30	11.02 ± 0.37	11.18 ± 0.31
36	10.79 ± 0.40	11.62 ± 0.29
	Intervention (n = 11)	**Control** (n = 11)

Table 4.24 Amplitude of accommodation at each visit (mean ± SEM). Intervention period shaded red

4.5.2.18 Lag of accommodation with spectacle correction

Main findings:

- Lag of accommodation with spectacle correction did not change over time ($F_{(6, 60)}$ = 2.222, P = 0.053).

Pairwise comparisons for between-visit analysis (see Figure 4.18 and Table 4.25) showed that lag of accommodation with spectacle correction did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 12-month timepoints (P = 1.000), 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), 24- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

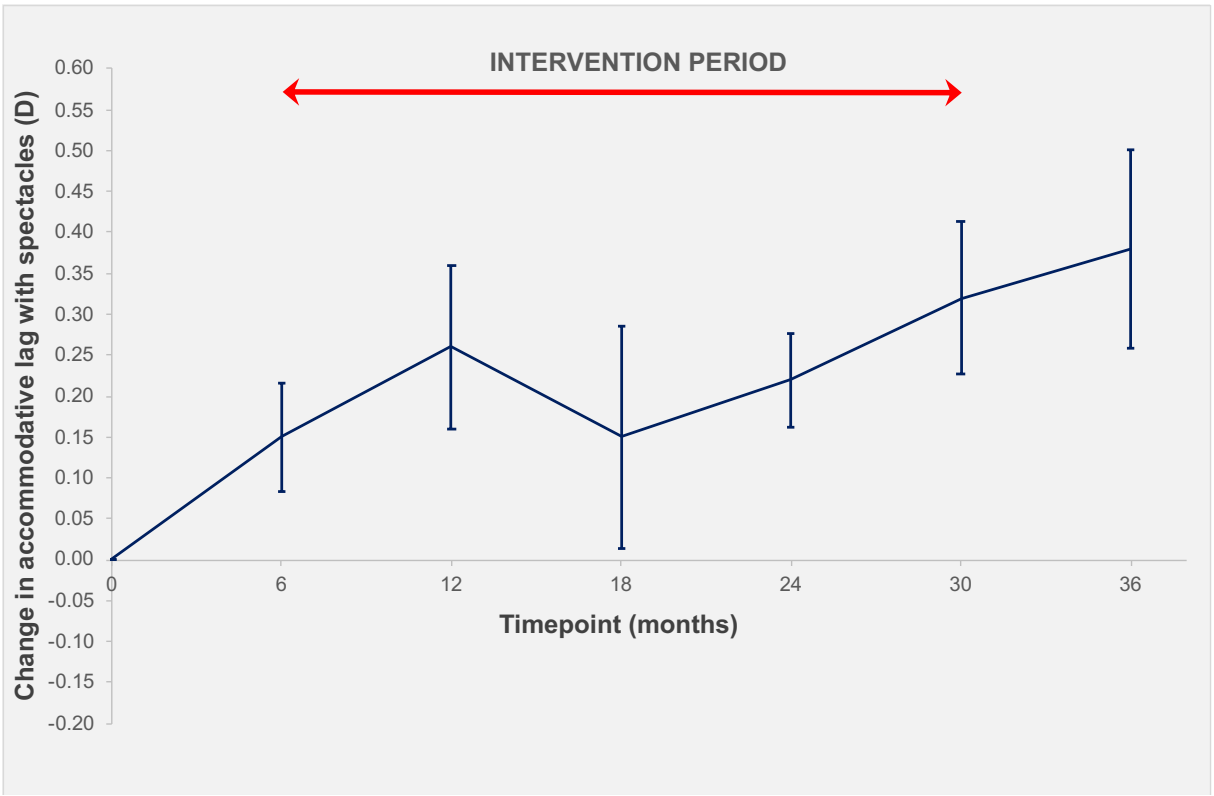

Figure 4.18 Change in accommodative lag with spectacle correction for a target at 0.33 m (mean ± SEM).

Timepoint (months)	**Accommodative lag** (D)
Baseline	0.78 ± 0.10
6	0.93 ± 0.06
12	1.04 ± 0.12
18	0.93 ± 0.12
24	1.00 ± 0.10
30	1.10 ± 0.08
36	1.16 ± 0.12
	Intervention (n = 11)

Table 4.25 Accommodative lag with spectacle correction for a target at 0.33 m (mean ± SEM). Intervention period shaded red

4.5.2.19 Lag of accommodation: spectacle correction *versus* CL correction

Main findings:

- Lag of accommodation was less with spectacle correction than CL correction ($F_{(1, 10)}$ = 20.845, P = 0.001) and did not change over time ($F_{(1, 10)}$ = 0.816, P = 0.388) with either form of correction ($F_{(1, 10)}$ = 0.096, P = 0.763).

Pairwise comparisons for between-visit analysis (see Table 4.26) showed that with spectacle correction, lag of accommodation was similar at the 12- and 24-month timepoints (P = 0.741).

Pairwise comparisons for between-visit analysis (see Table 4.26) showed that with CL correction, lag of accommodation was similar at the 12- and 24-month timepoints (P = 0.438).

Timepoint (months)	**Accommodative lag** (D)	
12	1.04 ± 0.12	1.70 ± 0.09
24	1.00 ± 0.10	1.60 ± 0.11
	Spectacles (n = 11)	**CLs** (n = 11)

Table 4.26 Accommodative lag with spectacle correction *versus* CL correction for a target at 0.33 m (mean ± SEM). Intervention period shaded red

4.5.2.20 Central CL power

Main findings:

- Central CL power reduced over time ($F_{(4, 40)} = 18.408$, $P < 0.0005$) for the intervention eye group only ($F_{(4, 40)} = 3.866$, $P = 0.010$).

Pairwise comparisons for between-visit analysis (see Figure 4.19 and Table 4.27) showed that for the intervention eye group, central CL power did not change between the 6- and 12-month timepoints (P = 0.119) but decreased between the 12- and 18-month timepoints (P = 0.019) and the 18- and 24-month timepoints (P = 0.039) but not between the 24- and 30-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.19 and Table 4.27) showed that for the control eye group, central CL power did not change between the 6- and 12-month timepoints (P = 0.531), nor between the 12- and 18-month timepoints (P = 0.251), the 18- and 24-month timepoints (P = 0.379) and the 24- and 30-month timepoints (P = 1.000).

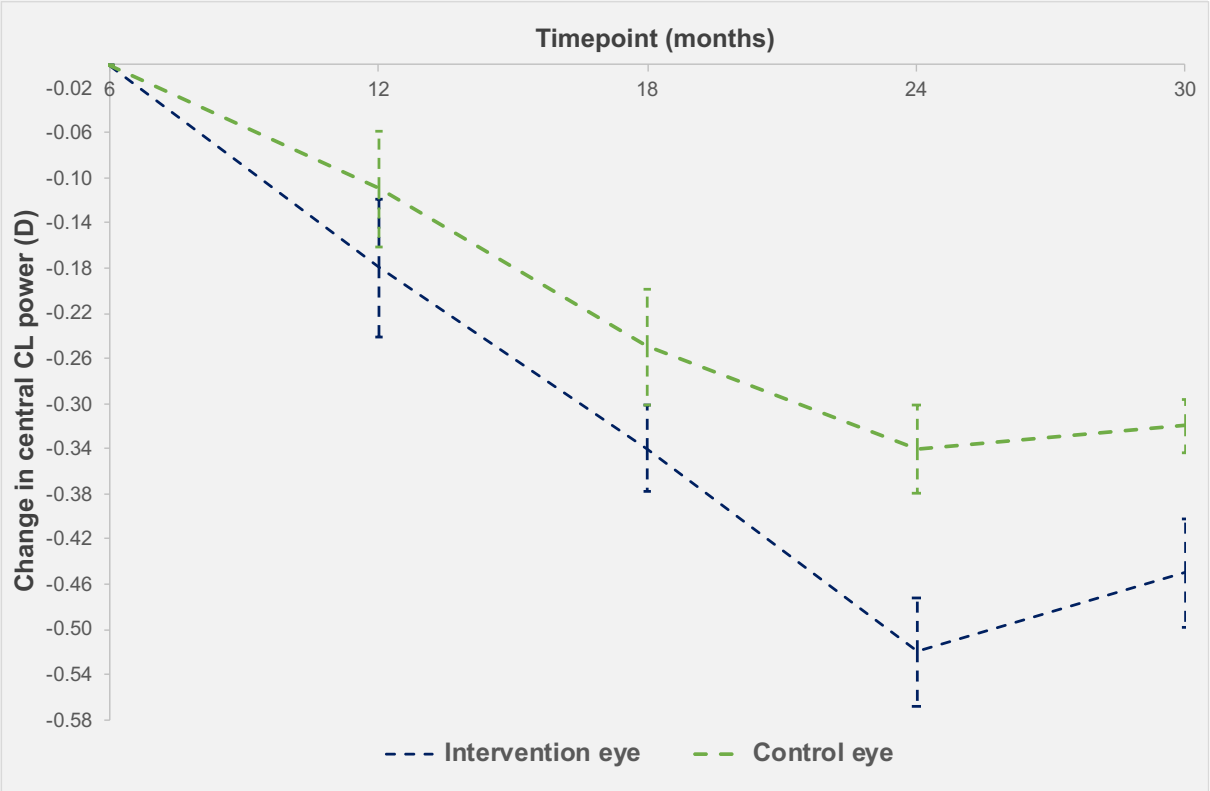

Figure 4.19 Change in central CL power (mean ± SEM)

Timepoint (months)	**Central CL power** (D)	
6	3.59 ± 0.42	2.00 ± 0.39
12	3.41 ± 0.44	1.89 ± 0.41
18	3.25 ± 0.46	1.75 ± 0.43
24	3.07 ± 0.43	1.66 ± 0.43
30	3.14 ± 0.47	1.68 ± 0.45
	Intervention (n = 11)	**Control** (n = 11)

Table 4.27 Central CL power (mean ± SEM)

4.5.2.21 CL WT

Main findings:

- CL WT changed over time ($F_{(4, 40)} = 4.476$, $P = 0.004$), increasing over the first 6 months of wear and then remained stable throughout the remainder of the intervention period.

Pairwise comparisons for between-visit analysis (see Figure 4.20 and Table 4.28) showed that mean weekly CL WT increased between the 6- and 12-month timepoints (P = 0.009), but not between the 12- and 18-month timepoints (P = 1.000), 18- and 24-month timepoints (P = 1.000), nor the 24- and 30-month timepoints (P = 1.000).

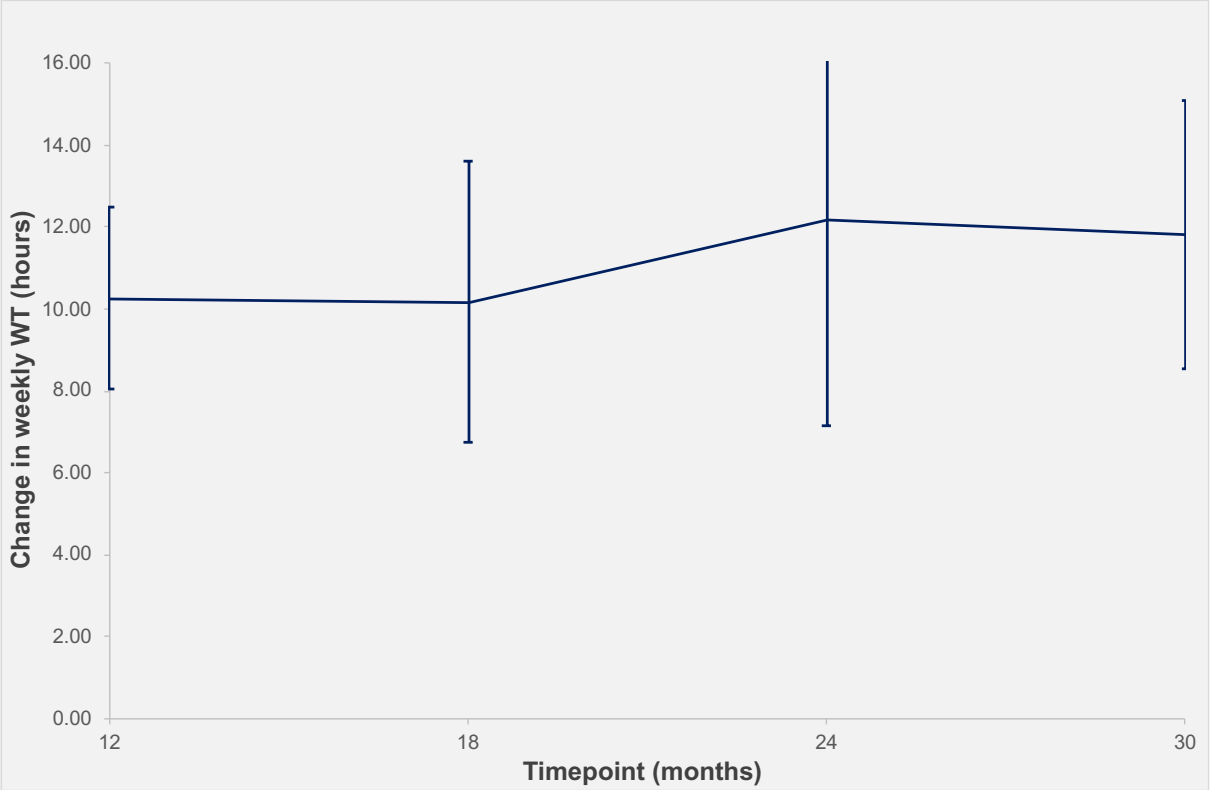

Figure 4.20 Change in typical weekly CL WT (mean ± SEM).

Timepoint (months)	**Weekly CL WT** (hours)
6	59.64 ± 1.98
12	69.91 ± 3.18
18	69.82 ± 3.26
24	71.82 ± 3.57
30	71.45 ± 2.67

Table 4.28 Typical weekly CL WT (mean ± SEM). Measures at the initial timepoint taken at the first CL aftercare visit

4.5.2.22 Peripheral refraction MSE

Main findings:

- MSE peripheral refraction was relatively myopic in the temporal, nasal, superior, and inferior quadrants in the intervention eye and control eye groups (see Table 4.29 and Table 4.30)
- Absolute values for central and peripheral refraction in all four quadrants are detailed in Figures 4.21 to 4.24.

	Relative peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-2.40 ± 0.46	-0.55 ± 0.48	-0.43 ± 0.27	-0.71 ± 0.13
6	-2.68 ± 0.54	-1.12 ± 0.44	-0.45 ± 0.32	-0.26 ± 0.27
18	-2.24 ± 0.64	-1.11 ± 0.52	-0.86 ± 0.45	-0.16 ± 0.34
30	-2.15 ± 0.70	-2.18 ± 0.81	-0.66 ± 0.40	-0.62 ± 0.17
36	-2.18 ± 0.76	-1.47 ± 0.66	-0.54 ± 0.41	-0.86 ± 0.12

Table 4.29 MSE post-cycloplegic relative peripheral refractive error at each visit for the intervention eye group (mean ± SEM). Intervention period shaded red

	Relative peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-1.45 ± 0.30	-0.39 ± 0.26	-0.36 ± 0.26	-0.21 ± 0.17
6	-1.81 ± 0.51	-0.69 ± 0.41	-0.41 ± 0.25	-0.05 ± 0.21
18	-1.27 ± 0.70	-0.96 ± 0.43	-0.52 ± 0.37	-0.36 ± 0.35
30	-1.27 ± 0.51	-0.98 ± 0.60	-0.56 ± 0.33	-0.60 ± 0.35
36	-1.50 ± 0.53	-0.94 ± 0.45	-0.60 ± 0.29	-0.52 ± 0.41

Table 4.30 MSE post-cycloplegic relative peripheral refractive error at each visit for the control eye group (mean ± SEM)

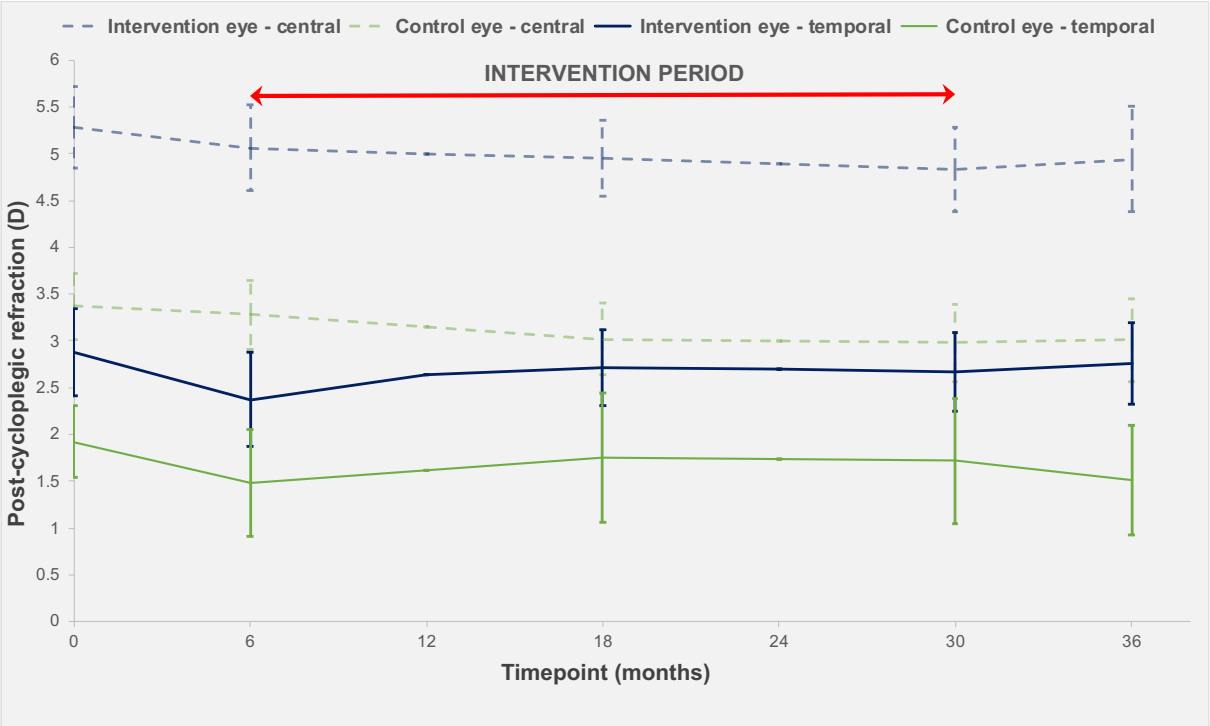

Figure 4.21 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 30° temporally (mean ± SEM)

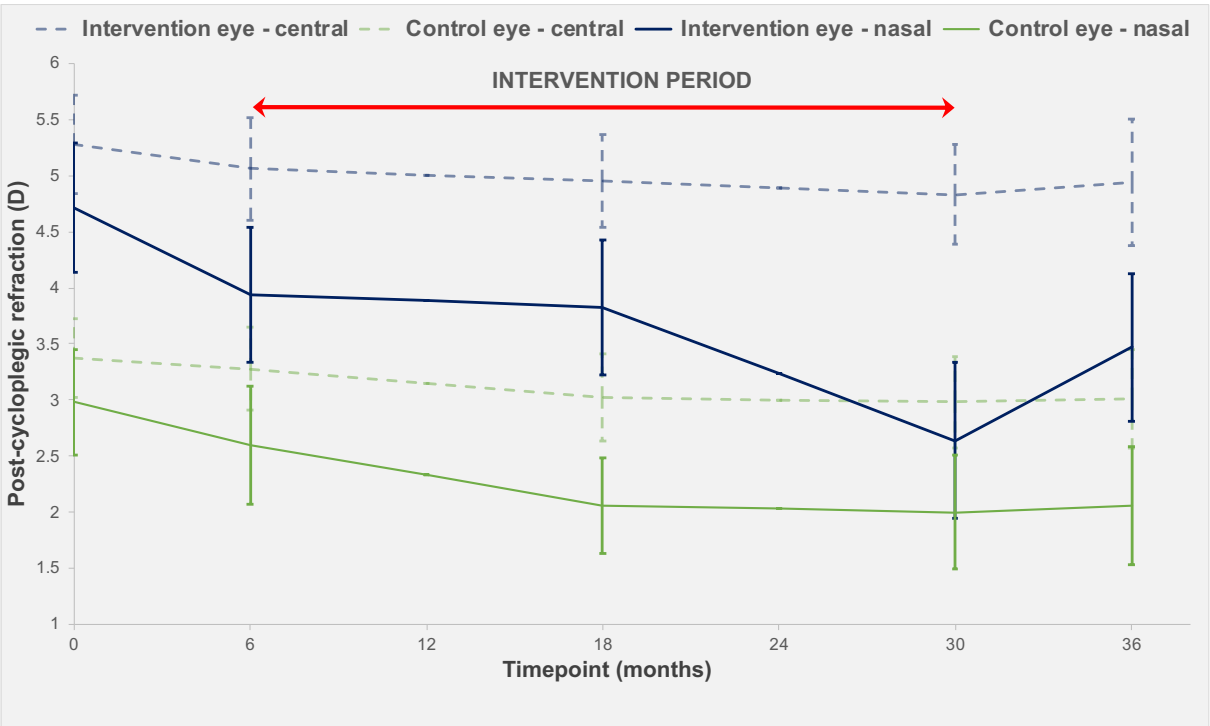

Figure 4.22 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 30° nasally (mean ± SEM)

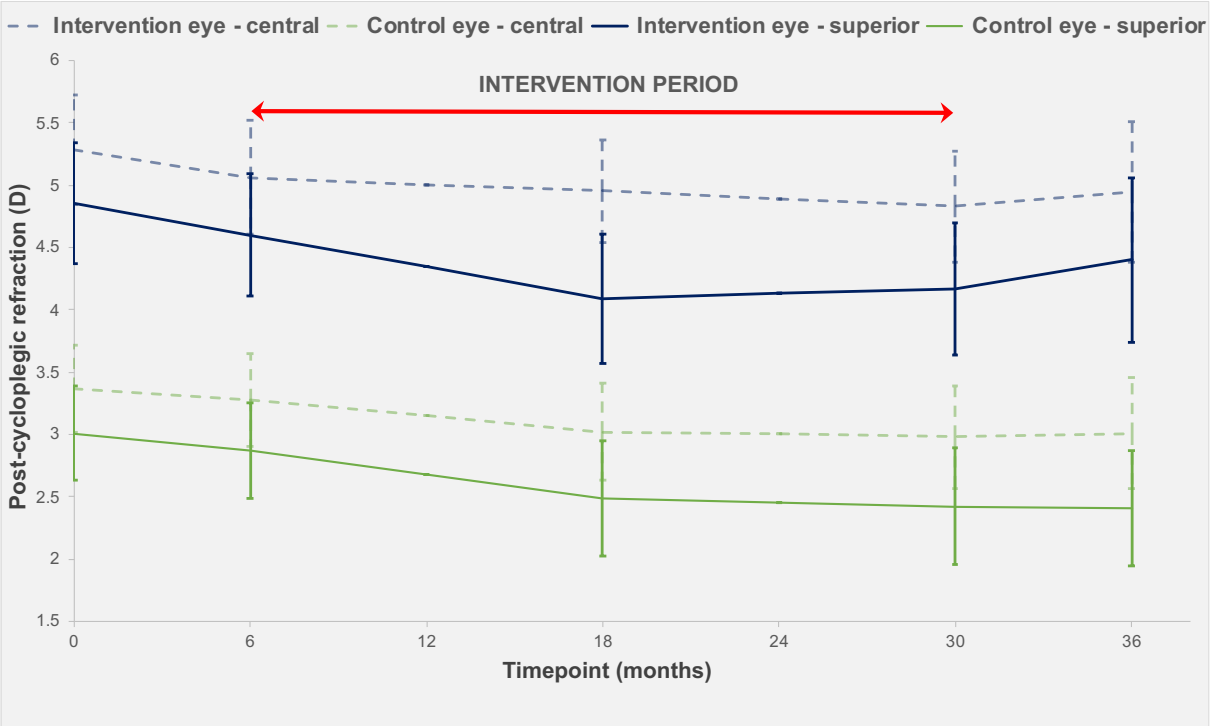

Figure 4.23 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 20° superiorly (mean ± SEM)

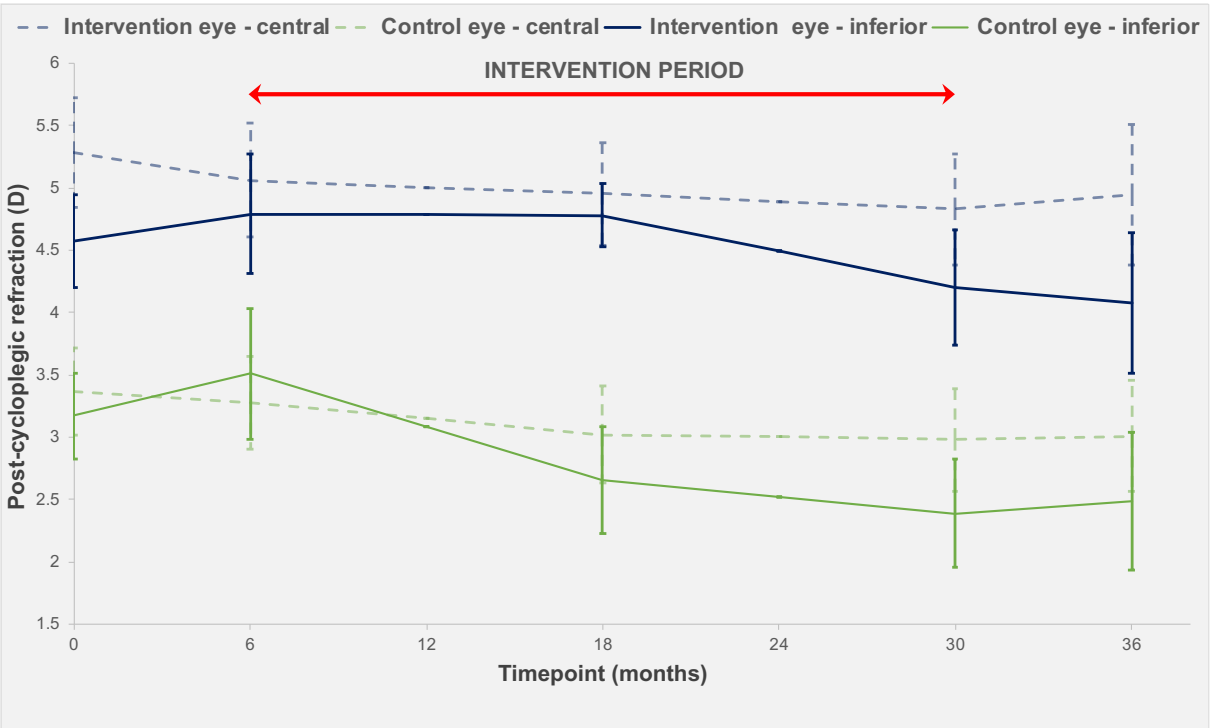

Figure 4.24 Absolute MSE post-cycloplegic central refraction compared to peripheral refraction at 20° inferiorly (mean ± SEM)

For the intervention eye group, relative MSE peripheral refraction varied by location ($F_{(3, 30)}$ = 6.179, P = 0.002) (See Figure 4.25). The temporal quadrant demonstrated a similar degree of relative myopia compared to the nasal (P = 0.186) and superior (P = 0.110) quadrants, respectively but was relatively more myopic than the inferior quadrant (P = 0.033). Relative MSE peripheral myopia in the nasal quadrant was similar to the superior (P = 1.000) and inferior (P = 0.822) quadrants; this was also the case when comparing the superior quadrant to the inferior quadrant (P = 1.000).

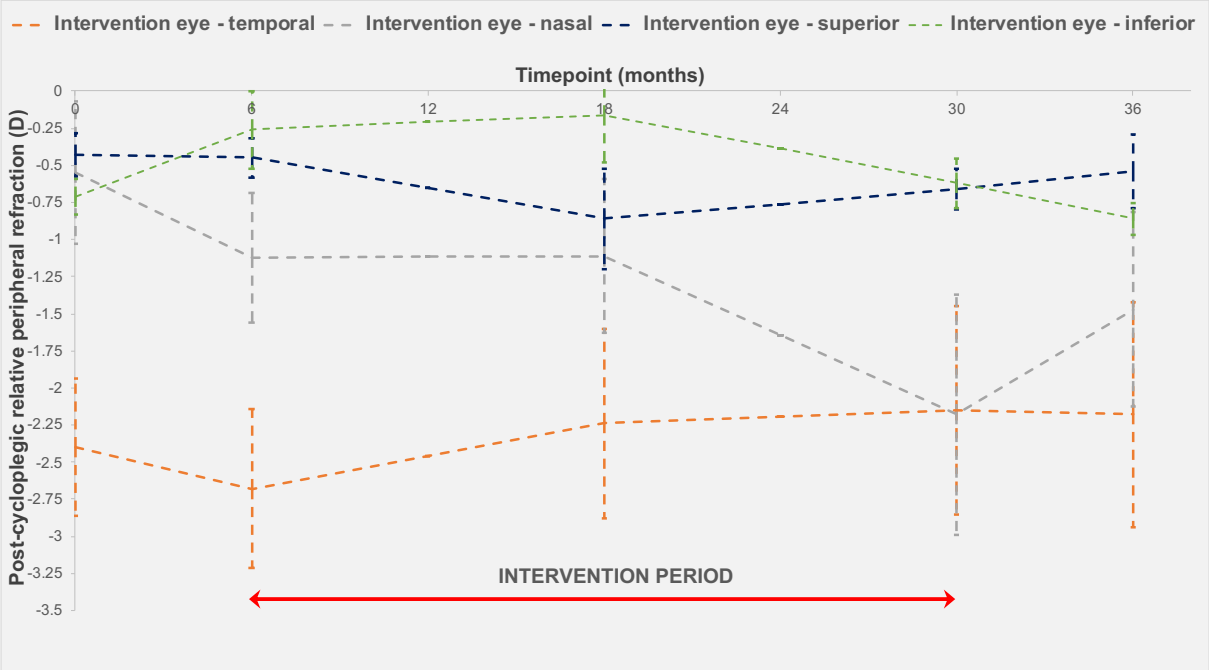

Figure 4.25 MSE post-cycloplegic relative peripheral refractive error at each visit for the intervention eye group (mean ± SEM)

For the control eye group, relative peripheral MSE refraction did not vary by location ($F_{(3, 30)}$ = 2.744, [Greenhouse-Geisser P = 0.104, Epsilon 0.613]) (See Figure 4.26). Relative peripheral MSE myopia in the temporal quadrant was similar to the nasal (P = 1.000), superior (P = 0.646), and inferior (P = 0.466) quadrants, respectively; this was also the case when comparing the nasal quadrant to the superior (P = 1.000) and the inferior quadrants (P = 1.000). The superior and inferior quadrants also had similar levels of relative peripheral MSE myopia (P = 1.000).

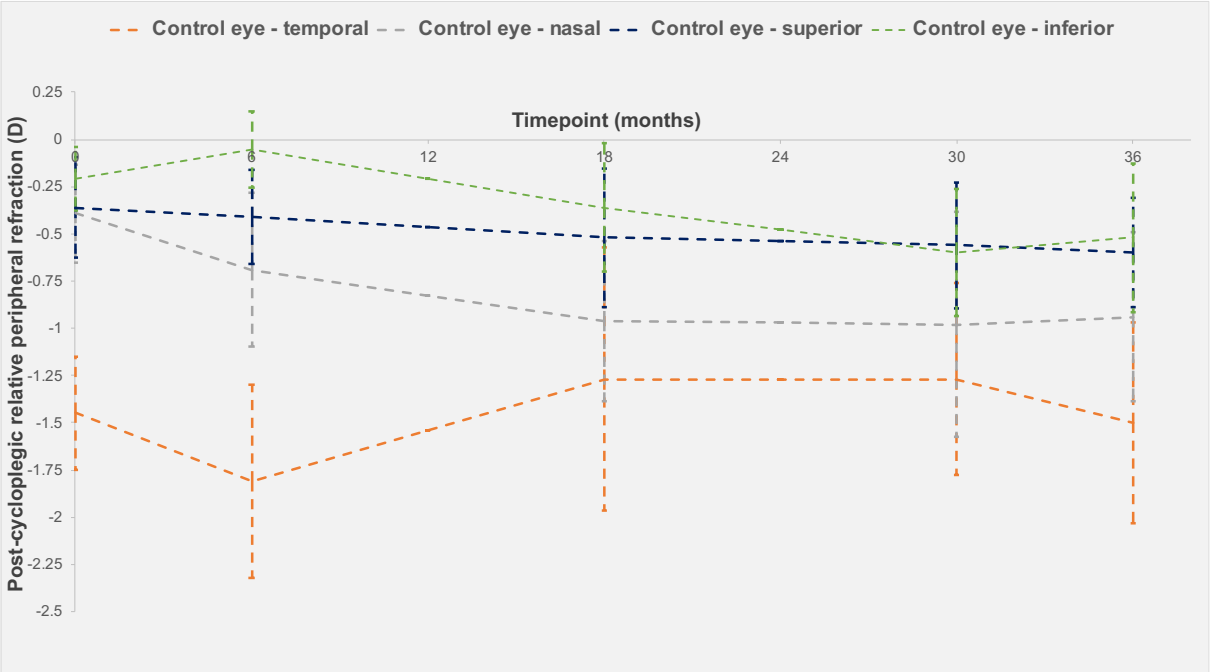

Figure 4.26 MSE post-cycloplegic relative peripheral refractive error at each visit for the control eye group (mean ± SEM)

Relative peripheral MSE refraction in the temporal quadrant was more myopic for the intervention eye group than the control eye group ($F_{(1, 10)}$ = 11.139, P = 0.008) and did not change over time ($F_{(4, 40)}$ = 0.825, P = 0.517) in either group ($F_{(4, 40)}$ = 0.087, P = 0.986).

Pairwise comparisons for between-visit analysis (see Figures 4.21 and 4.25, and Table 4.29) showed that for the intervention eye group, relative peripheral MSE refraction in the temporal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figures 4.21 and 4.26, and Table 4.30) showed that for the control eye group, relative peripheral MSE refraction in the temporal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Relative peripheral MSE refraction in the nasal quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 2.463, P = 0.148) and did not change over time ($F_{(4, 40)}$ = 2.522, P = 0.056) in either group ($F_{(4, 40)}$ = 1.197, P = 0.327).

Pairwise comparisons for between-visit analysis (see Figures 4.22 and 4.25, and Table 4.29) showed that for the intervention eye group, relative peripheral MSE refraction in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 0.488), nor between the 6- and 18-month timepoints (P = 0.511), 18- and 30-month timepoints (P = 0.651) and the 30- and 36-month timepoints (P = 0.696).

Pairwise comparisons for between-visit analysis (see Figures 4.22 and 4.26, and Table 4.30) showed that for the control eye group, relative peripheral MSE refraction in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Relative peripheral MSE refraction in the superior quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 0.550, P = 0.476) and did not change over time ($F_{(4, 40)}$ = 0.632, P = 0.642) in either group ($F_{(4, 40)}$ = 0.844 P = 0.506).

Pairwise comparisons for between-visit analysis (see Figures 4.23 and 4.25, and Table 4.29) showed that for the intervention eye group, relative peripheral MSE refraction in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figures 4.23 and 4.26, and Table 4.30) showed that for the control eye group, relative peripheral MSE refraction in the superior

quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Relative peripheral MSE refraction in the inferior quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 0.666, P = 0.433) and did not change over time ($F_{(4, 40)}$ = 1.434, P = 0.240) in either group ($F_{(4, 40)}$ = 1.125 P = 0.359).

Pairwise comparisons for between-visit analysis (see Figures 4.23 and 4.25, and Table 4.29) showed that for the intervention eye group, relative peripheral MSE refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 0.877), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figures 4.24 and 4.26, and Table 4.30) showed that for the control eye group, relative peripheral MSE refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

4.5.2.23 Peripheral refraction (J0)

Main findings:

- For the intervention eye group, J0 peripheral refraction varied by location ($F_{(3, 30)}$ = 10.933, [Greenhouse-Geisser P = 0.002, Epsilon 0.618]) (See Figure 4.27). The temporal quadrant was similar to the nasal quadrant (P = 0.148) but relatively more myopic than the superior (P = 0.005), and inferior (P = 0.014) quadrants, respectively. The nasal quadrant was similar to the superior (P = 0.206) and inferior (P = 0.392) quadrants, respectively. The superior and inferior quadrants were also similar to each other (P = 0.859).
- For the control eye group, mean J0 peripheral refraction varied by location ($F_{(3, 30)}$ = 14.319, [Greenhouse-Geisser P < 0.0005, Epsilon 0.711]) (See Figure 4.28). The temporal quadrant was similar to the nasal quadrant (P = 0.129) but relatively more myopic than both the superior (P = 0.005), and inferior (P = 0.008) quadrants. The nasal quadrant was similar to the superior (P = 0.069) and inferior (P = 0.130) quadrants, respectively. The superior and inferior quadrants were also similar to each other (P = 0.598).

J0 peripheral refraction in the temporal quadrant was similar for the intervention eye and control eye groups, respectively ($F_{(1, 10)}$ = 0.394, P = 0.544) and did not change over time ($F_{(4, 40)}$ = 0.976, P = 0.431) in either group ($F_{(4, 40)}$ = 0.123, P = 0.974).

Pairwise comparisons for between-visit analysis (see Figure 4.27 and Table 4.31) showed that for the intervention eye group, measures in the temporal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.28 and Table 4.32) showed that for the control eye group, measures in the temporal quadrant did not change from baseline to

the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

J0 peripheral refraction in the nasal quadrant was similar for the intervention eye and control eye groups, respectively ($F_{(1, 10)}$ = 1.254, P = 0.289) and changed over time ($F_{(4, 40)}$ = 3.355, P = 0.018) in both groups ($F_{(4, 40)}$ = 1.167, P = 0.340).

Pairwise comparisons for between-visit analysis (see Figure 4.27 and Table 4.31) showed that for the intervention eye group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.116) and the 30- and 36-month timepoints (P = 0.897).

Pairwise comparisons for between-visit analysis (see Figure 4.28 and Table 4.32) showed that for the control eye group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000), and the 30- and 36-month timepoints (P = 1.000).

J0 peripheral refraction in the superior quadrant was similar for the intervention eye and control eye groups, respectively ($F_{(1, 10)}$ = 4.51, P = 0.060) and changed over time ($F_{(4, 40)}$ = 3.216, P = 0.022) in both groups ($F_{(4, 40)}$ = 0.440, P = 0.779).

Pairwise comparisons for between-visit analysis (see Figure 4.27 and Table 4.31) showed that for the intervention eye group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.28 and Table 4.32) showed that for the control eye group, measures in the superior quadrant did not change from baseline to

the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000). There was a change between the 18- and 30-month timepoints (P = 0.032) but not between the 30- and 36-month timepoints (P = 1.000).

J0 peripheral refraction in the inferior quadrant was similar for the intervention eye and control eye groups, respectively ($F_{(1, 10)}$ = 2.285, P = 0.162) and did not change over time ($F_{(4, 40)}$ = 0.644, P = 0.634) in either group ($F_{(4, 40)}$ = 0.536 P = 0.710).

Pairwise comparisons for between-visit analysis (see Figure 4.27 and Table 4.31) showed that for the intervention eye group, measures in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.28 and Table 4.32) showed that for the control eye group, relative peripheral refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°

Baseline	-1.48 ± 0.31	-0.29 ± 0.20	0.32 ± 0.12	0.24 ± 0.19
6	-1.79 ± 0.29	-0.38 ± 0.31	0.37 ± 0.18	0.27 ± 0.14
18	-1.59 ± 0.37	-0.61 ± 0.37	0.40 ± 0.23	-0.08 ± 0.27
30	-1.24 ± 0.46	-1.39 ± 0.55	0.16 ± 0.16	-0.05 ± 0.32
36	-1.19 ± 0.48	-0.98 ± 0.48	0.13 ± 0.14	0.20 ± 0.20

Table 4.31 J0 post-cycloplegic peripheral refractive error at each visit for the intervention eye group (mean ± SEM). Intervention period shaded red

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	-1.47 ± 0.22	-0.15 ± 0.14	0.43 ± 0.12	0.36 ± 0.11
6	-1.60 ± 0.42	-0.41 ± 0.30	0.67 ± 0.16	0.36 ± 0.18
18	-1.31 ± 0.59	-0.58 ± 0.34	0.63 ± 0.10	0.35 ± 0.09
30	-1.20 ± 0.45	-0.71 ± 0.40	0.33 ± 0.11	0.22 ± 0.15
36	-1.20 ± 0.51	-0.69 ± 0.35	0.22 ± 0.09	0.28 ± 0.15

Table 4.32 J0 post-cycloplegic peripheral refractive error at each visit for the control eye group (mean ± SEM)

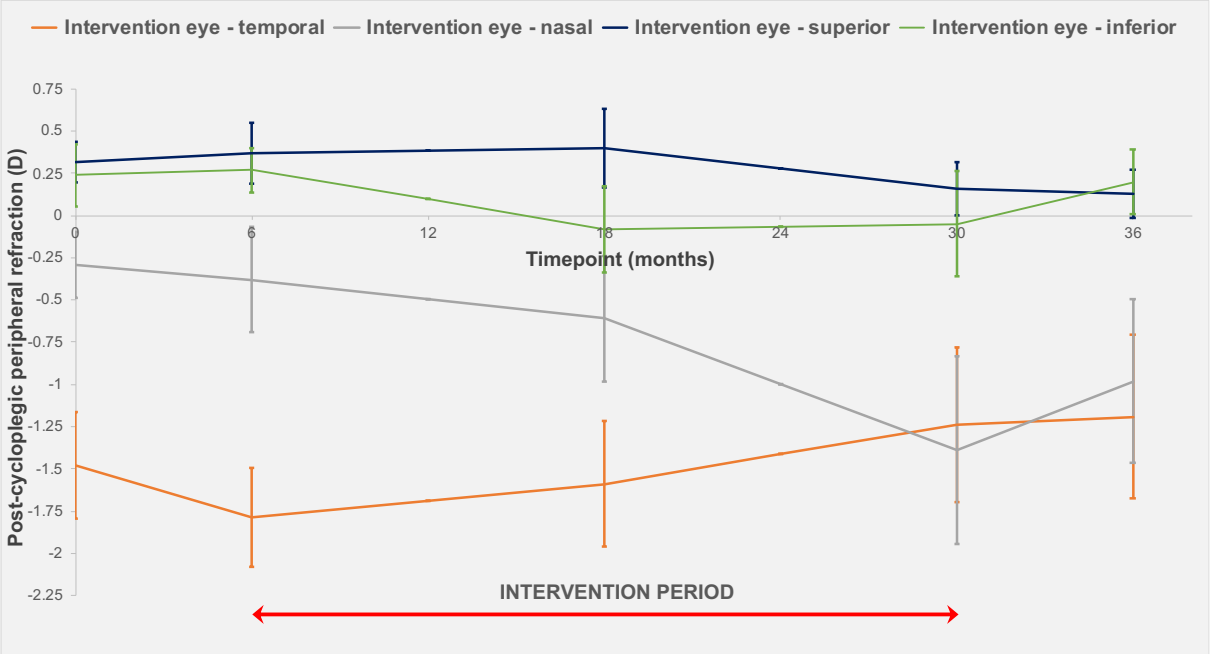

Figure 4.27 J0 post-cycloplegic peripheral refractive error at each visit for the intervention eye group (mean ± SEM)

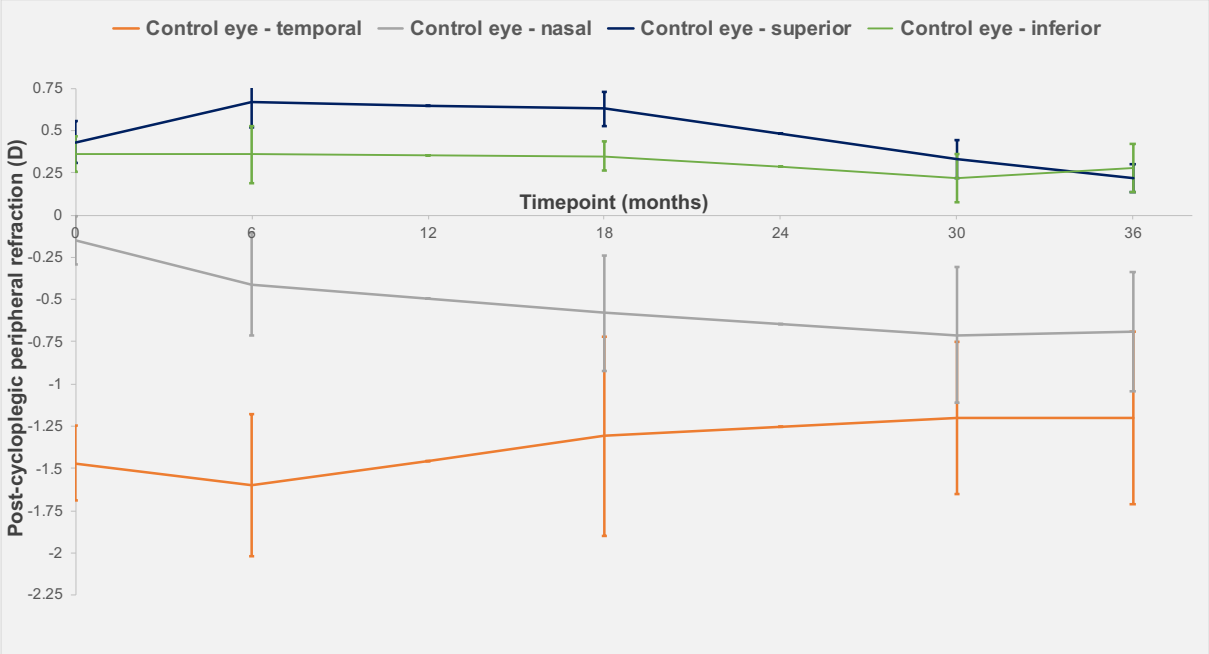

Figure 4.28 J0 post-cycloplegic peripheral refractive error at each visit for the control eye group (mean ± SEM)

4.5.2.24 Peripheral refraction (J45)

Main findings:

- For the intervention eye group, J45 peripheral refraction for the intervention eye group was similar in all locations ($F_{(3, 30)} = 0.612$, P = 0.613) (See Figure 4.29). The temporal quadrant was similar to the nasal (P = 1.000), superior (P = 1.00), and inferior (P = 1.000) quadrants, respectively. The nasal quadrant was similar to the superior (P = 1.000) and inferior (P = 1.000) quadrants, respectively. The superior quadrant was also similar to the superior quadrant (P = 1.000).

- For the control eye group, J45 peripheral refraction was similar in all locations ($F_{(3, 30)}$ = 0.905, P = 0.450) (See Figure 4.30). The temporal quadrant was similar to the nasal (P = 1.000), superior (P = 1.00), and inferior (P = 1.000) quadrants, respectively. The nasal quadrant was similar to the superior (P = 1.000) and inferior (P = 1.000) quadrants, respectively. The superior quadrant was also similar to the superior quadrant (P = 1.000).

J45 peripheral refraction in the temporal quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 0.319, P = 0.585) and did not change over time ($F_{(4, 40)}$ = 1.320, P = 0.279) in either group ($F_{(4, 40)}$ = 3.822, P = 0.100).

Pairwise comparisons for between-visit analysis (see Figure 4.29 and Table 4.33) showed that for the intervention eye group, measures in the temporal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.078) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.30 and Table 4.34) showed that for the control eye group, measures in the temporal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.659) and the 30- and 36-month timepoints (P = 1.000).

J45 peripheral refraction in the nasal quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 2.296, P = 0.161) and did not change over time ($F_{(4, 40)}$ = 0.262, P = 0.901) in either group ($F_{(4, 40)}$ = 2.396, P = 0.066).

Pairwise comparisons for between-visit analysis (see Figure 4.29 and Table 4.33) showed that for the intervention eye group, measures in the nasal quadrant did not change from baseline

to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.30 and Table 4.34) showed that for the control eye group, measures in the nasal quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

J45 peripheral refraction in the superior quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 0.309, P = 0.590) and did not change over time ($F_{(4, 40)}$ = 1.357, P = 0.266) in either group ($F_{(4, 40)}$ = 1.491, P = 0.223).

Pairwise comparisons for between-visit analysis (see Figure 4.29 and Table 4.33) showed that for the intervention eye group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.30 and Table 4.34) showed that for the control eye group, measures in the superior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 1.000) and the 30- and 36-month timepoints (P = 1.000).

J45 peripheral refraction in the inferior quadrant was similar for the intervention eye and control eye groups ($F_{(1, 10)}$ = 1.670, P = 0.225) and did not change over time ($F_{(4, 40)}$ = 1.318, P = 0.280) in either group ($F_{(4, 40)}$ = 0.298, P = 0.878).

Pairwise comparisons for between-visit analysis (see Figure 4.29 and Table 4.33) showed that for the intervention eye group, measures in the inferior quadrant did not change from baseline

to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.363) and the 30- and 36-month timepoints (P = 1.000).

Pairwise comparisons for between-visit analysis (see Figure 4.30 and Table 4.34) showed that for the control eye group, relative peripheral refraction in the inferior quadrant did not change from baseline to the 6-month timepoint (P = 1.000), nor between the 6- and 18-month timepoints (P = 1.000), 18- and 30-month timepoints (P = 0.517) and the 30- and 36-month timepoints (P = 1.000).

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	0.13 ± 0.08	0.08 ± 0.09	0.11 ± 0.07	0.07 ± 0.08
6	-0.03 ± 0.15	0.02 ± 0.10	-0.14 ± 0.16	0.09 ± 0.09
18	-0.07 ± 0.13	0.22 ± 0.11	0.10 ± 0.06	0.27 ± 0.17
30	0.36 ± 0.17	0.21 ± 0.09	0.00 ± 0.10	0.04 ± 0.20
36	0.38 ± 0.15	0.28 ± 0.13	0.10 ± 0.06	0.15 ± 0.11

Table 4.33 J45 post-cycloplegic peripheral refractive error at each visit for the intervention eye group (mean ± SEM). Intervention period shaded red

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
Baseline	0.03 ± 0.15	0.09 ± 0.13	0.20 ± 0.10	-0.12 ± 0.09
6	0.06 ± 0.15	-0.01 ± 0.13	0.14 ± 0.12	0.00 ± 0.09
18	0.27 ± 0.09	-0.17 ± 0.16	0.04 ± 0.10	0.23 ± 0.09
30	-0.09 ± 0.15	-0.14 ± 0.13	0.08 ± 0.06	-0.10 ± 0.15
36	0.01 ± 0.11	-0.20 ± 0.14	0.03 ± 0.06	-0.05 ± 0.11

Table 4.34 J45 post-cycloplegic peripheral refractive error at each visit for the control eye group (mean ± SEM)

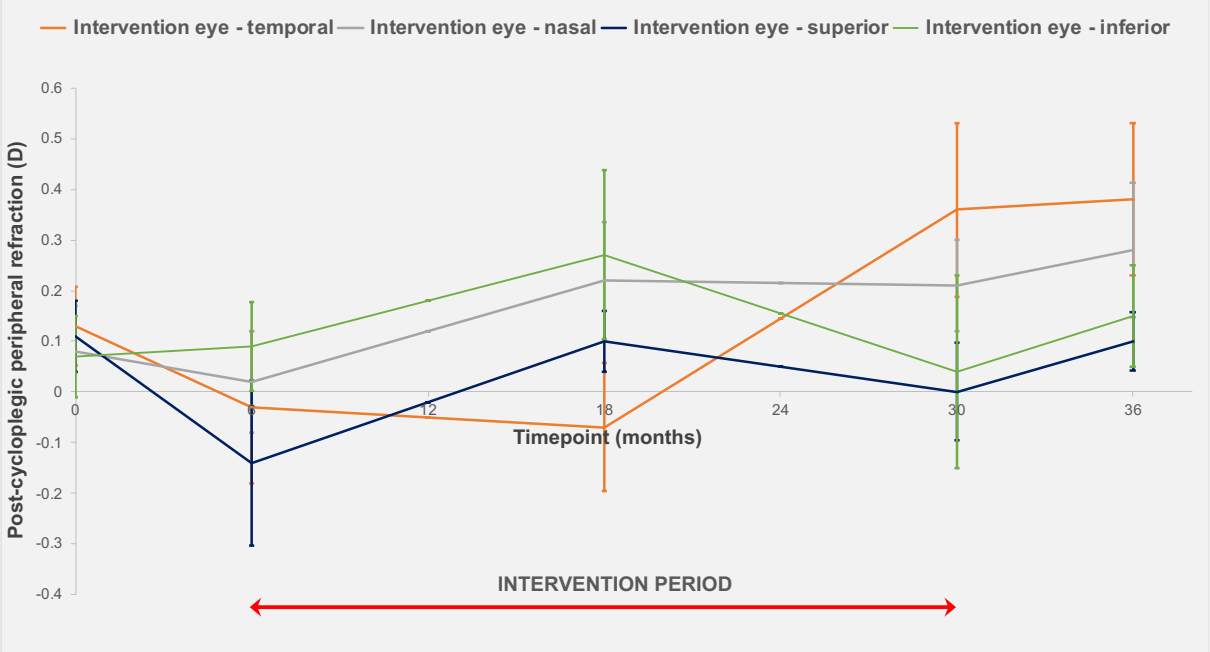

Figure 4.29 J45 post-cycloplegic peripheral refractive error at each visit for the intervention eye group (mean ± SEM)

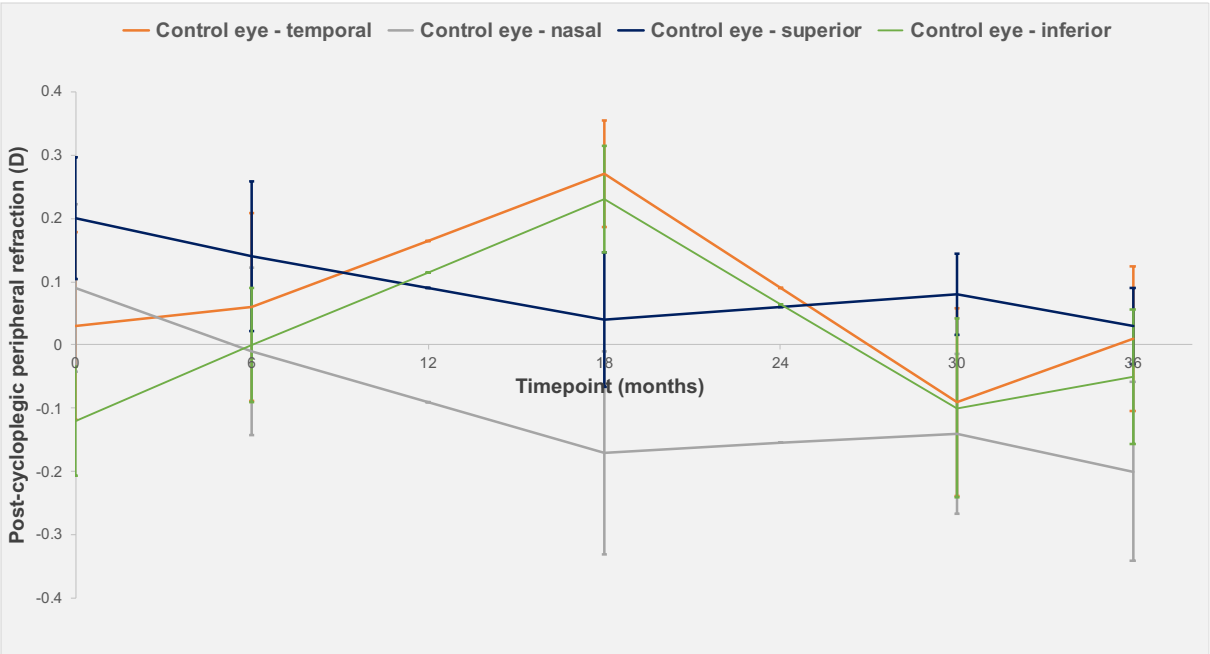

Figure 4.30 J45 post-cycloplegic peripheral refractive error at each visit for the control eye group (mean ± SEM)

4.5.2.25 Relative peripheral refraction with CL *in situ*

Main findings:

- Non-cycloplegic peripheral refraction with CL correction in situ demonstrated more relative hyperopia in the intervention eye group than the control eye group ($F_{(1, 10)}$ = 25.425, P = 0.001) and varied by location ($F_{(3, 30)}$ = 5.604, P = 0.004) in both groups ($F_{(3, 30)}$ = 0.592, P = 0.625).

Pairwise comparisons (see Figure 4.31 and Table 4.35) for the intervention eye group showed that the temporal quadrant was similar to the nasal quadrant (P = 1.000) and the inferior quadrant (P = 0.375) but was relatively more hyperopic than the superior quadrant (P = 0.021). The nasal quadrant demonstrated a similar degree of relative hyperopia to the superior (P = 0.408) and inferior quadrants (P = 0.016), while the superior and inferior quadrants were also similar to each other (P = 1.000).

Pairwise comparisons (see Figure 4.32 and Table 4.36) for the control eye group showed that the temporal quadrant was similar to the nasal (P = 1.000), superior (P = 0.056) and the inferior quadrants (P = 0.807). The nasal quadrant demonstrated a similar degree of relative hyperopia to the superior (P = 0.404) and inferior quadrants (P = 1.000), while the superior and inferior quadrants were also similar to each other (P = 1.000).

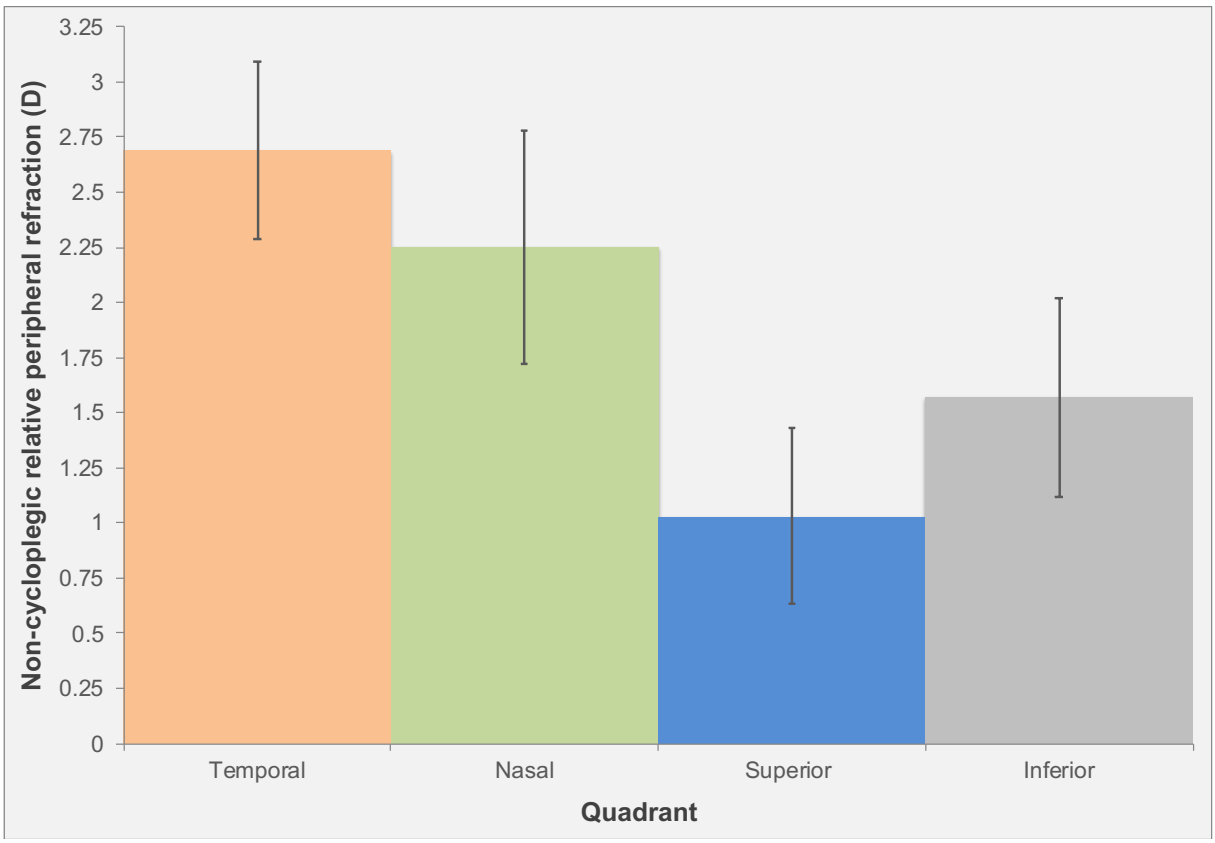

Figure 4.31 MSE non-cycloplegic relative peripheral refraction with CL correction *in situ* for the intervention eye group (mean ± SEM)

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
12	2.69 ± 0.40	2.25 ± 0.53	1.03 ± 0.40	1.57 ± 0.45

Table 4.35 MSE non-cycloplegic relative peripheral refraction with CL correction *in situ* for the intervention eye group (mean ± SEM)

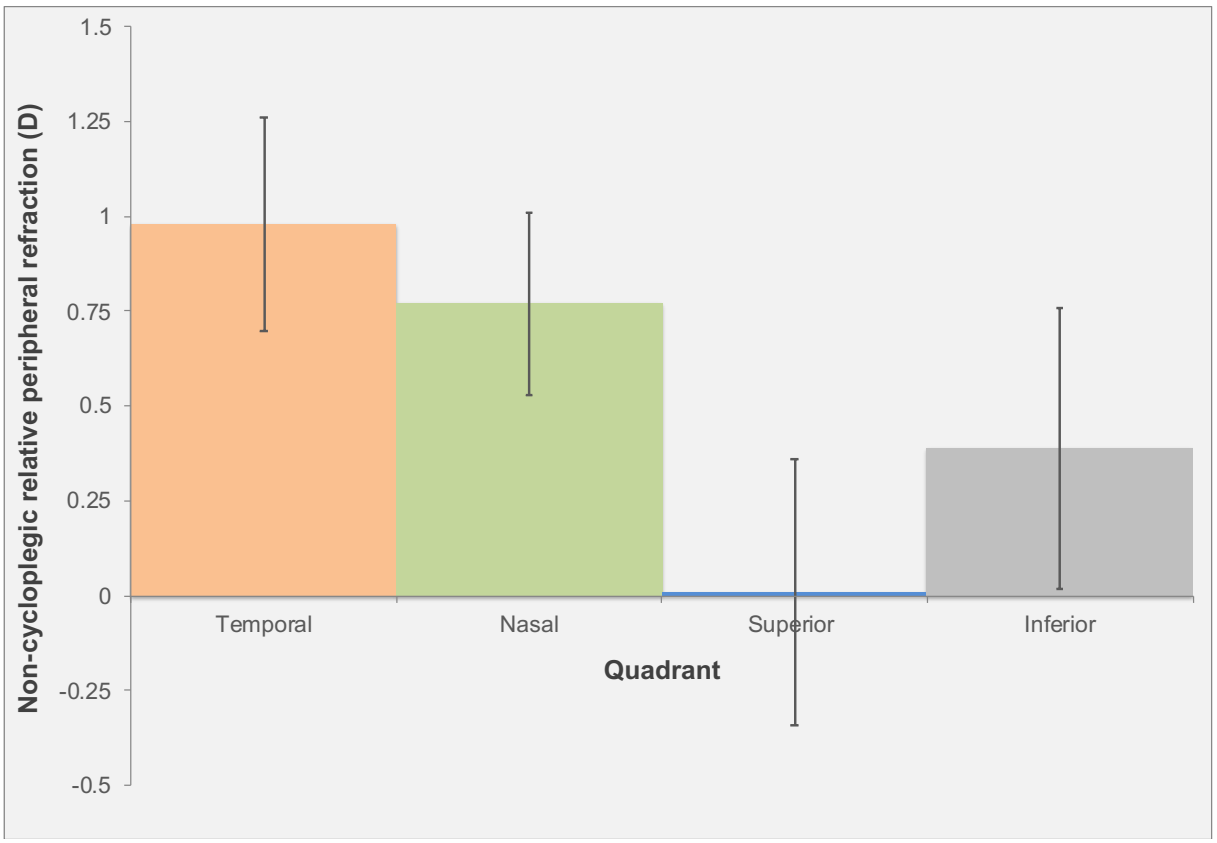

Figure 4.32 MSE non-cycloplegic relative peripheral refraction with CL correction *in situ* for the control eye group (mean ± SEM)

	Peripheral refraction (D)			
Timepoint (months)	Temporal 30°	Nasal 30°	Superior 20°	Inferior 20°
12	0.98 ± 0.28	0.77 ± 0.24	0.01 ± 0.35	0.39 ± 0.37

Table 4.36 MSE non-cycloplegic relative peripheral refraction with CL correction *in situ* for the control eye group (mean ± SEM)

4.6 Discussion

The work outlined in this paired-eye clinical trial has explored for the first time if anisometropia can be reduced in anisohyperopes by imposing RPHD unilaterally in the more hyperopic eye, with the fellow eye serving as a control. The first of two primary outcome measures, axial growth, showed that despite the imposition of RPHD, AL did not increase significantly over time in the intervention eye. Intriguingly, AL in the control eye did increase over the trial period,

and in fact, the interocular difference in AL was greater at the point of exit from the trial than at baseline. The findings here are in contrast to the work outlined in Chapter 3 for isohyperopes where axial growth in the intervention group outperformed the control group during the intervention period. The outcome from the present study may be considered unsurprising given recently published work demonstrating that, even at a small degree, anisometropia appears to disrupt the regulation of eye growth (Flitcroft *et al*., 2020).

For the second primary outcome measure, post-cycloplegic refractive error, once again results did not align with the original hypothesis. While mean refractive error decreased over time, this was by a similar amount in both the intervention and control eye group with a failure to close the gap between the interocular difference measured at baseline compared to the final outcome. As with the findings in Chapter 3, unlike AL, this outcome measure did not achieve statistical power. Once again, data could have been collected at each of the 7 timepoints to increase power but decisions such as these need to be considered alongside the burden placed upon young participants and potential impact upon drop out. Based upon the effect size, it is estimated that to achieve statistical power at 80% over 5 data collection points, a sample size of 49 participants would be required.

For secondary outcome measures, the longitudinal changes for anisohyperopes were broadly in keeping with their isohyperopic counterparts (see Chapter 3). For instance, while unaided DV was better in the control eye than the intervention eye group, this parameter did not change over time. Although statistically, spectacle DVA worsened over time in both the control eye and intervention eye groups, this was limited to 0.03 LogMAR units from baseline to exit measures so is, therefore, of limited clinical relevance, particularly taking into account the variability seen at interim visits. DVA was better with spectacles than CLs although there was greater improvement with the latter form of correction over time. Interestingly, improvements over time in DVA with CLs were similar in both the intervention (MF) wearers as the control (SV) wearers suggesting that adaptation may relate more to the CL itself rather

than the optics of the different designs. Measures of NVA with CLs also improved over time in both the intervention eye and control eye groups. Stereoacuity with spectacles did not change over time; however, unlike the isohyperopes in Chapter 3, stereoacuity was similar with spectacles and CLs which may be a result of reduced image degradation with unilateral MF optics in the anisohyperopic cohort. In terms of CS, once again, as with isohyperopes, measures were similar with spectacles compared to CLs in both SV and MF designs and did not change over time; this offers reassurance that visual performance with both unilateral and bilateral MF CLs is adequate for young wearers, which is borne out in the low levels of drop out witnessed throughout the studies outlined in both chapters. Neither CC nor ACD changed over time in either group, with the latter suggesting that the longitudinal increase in AL seen in the control eye group was likely to be due to VCD changes. In terms of accommodative function, lag with spectacle correction in the intervention eye did not change over time although it was significantly greater when compared to CLs; this finding could be important given that in myopic work, impaired lag has been implicated as a driver for axial growth and myopia progression (Mutti *et al*., 2006; Chakraborty *et al*., 2020) although it does not appear to be the case here. Paradoxically, given the findings for post-cycloplegic spectacle refraction, central CL power reduced over time in the intervention eye group but not the control eye group. Nevertheless, this may be accounted for by virtue of CL power being assessed under non-cycloplegic conditions.

All participants completed the trial, reinforcing the findings from Chapter 3 that young wearers can successfully transition into CL wear and also adapt well to wearing a MF design unilaterally. As outlined in Chapter 3, a potential limitation is the use of self-reported wearing times as the basis for presumed compliance. However, as with isohyperopes, the participants here were also, on the whole, reluctant to give up CLs at the end of the intervention period with the majority intending to resume wear upon exiting the study, which suggests that compliance was in line with reported values.

As with isohyperopes in Chapter 3, peripheral refraction was relatively myopic in all four quadrants in both the intervention eye and control eye groups and did not change over time. Importantly, relative peripheral refraction with CL *in situ* neatly demonstrated that centre-near MF CLs are a viable method to induce the desired defocus in anisohyperopes with a greater degree of RPH seen in the intervention eye group compared to the SV CL-wearing control eye group. However, regardless of this, as outlined in the discussion for isohyperopes, the role of peripheral defocus in the manipulation of axial growth remains uncertain and the primary outcomes here for anisohyperopes fails to add clarity. While the imposition of relative peripheral hyperopic defocus appears to influence growth rates in isohyperopes the same does not hold true for anisohyperopes using the paradigm outlined in the present work. It seems that, unlike isohyperopes, the unique growth patterns typically experienced by anisohyperopes are resistant to the influence of RPHD, at least in this age demographic and at the magnitude imposed here. It remains to be seen if earlier intervention and a more aggressive approach to defocus would yield more promising results; this provides an opportunity for future work with the aim to remedy the impact of near lifelong visual impairment these individuals would otherwise face. Instinctively, for anisohyperopes, the eye closer to emmetropia, in this case the control, would be considered the 'normal' eye. However, given that the mean growth rate for the more hyperopic eye is closer to the expected norm (Breslin *et al*., 2013), perhaps the control eye should be considered to be the 'abnormal' one of the pair. Redefining the eye in this way could change the approach to refractive error modulation in anisohyperopes where the primary endeavour would be to slow down growth in the *least* hyperopic eye rather than attempting to accelerate growth in the more hyperopic eye. To stretch this concept further, perhaps imposing competing defocus models could yield the greatest result, that is to say, using myopic defocus to slow down growth in the least hyperopic eye, with the opposite approach taken in the fellow eye.

5.0 Time course and repeatability of objective refraction and biometry following cycloplegia

5.1 Introduction

Refractive error modulation studies typically report changes to AL and post-cycloplegic refraction as the key outcome measures to determine the effect of a given intervention. With this in mind, it is important to understand the sensitivity of these measures in order to have confidence that any changes have arisen as a result of the intervention rather than any inherent variability in the clinical techniques that can occur between visits.

To date, refractive modulation studies in humans have primarily focused on myopes (see Chapter 1). Within a hyperopic cohort, particularly in young participants, it is possible that fluctuations in accommodation could play a greater role in measurement variability compared to their myopic counterparts given that they are likely to spend time without refractive correction and may not have their full manifest refractive error corrected (Leat, 2011).

The Zeiss IOLMaster 500 is considered ideal for the purposes of AL monitoring (see Chapter 2) with good repeatability. Lam *et al.*, 2002 reported a mean difference between measures taken on the same day of 0.0042 mm in a young, adult, myopic cohort under non-cycloplegic conditions with 95% limits of agreement (LoA) of ± 0.047 mm. Others concur, reporting high repeatability of non-cycloplegic AL measurement in adults (Santodomingo-Rubido *et al*., 2002;); these measures are also repeatable for children in both mixed (Hussin *et al*., 2006) and myopic refractive cohorts under non-cycloplegic conditions (Kimura *et al*., 2007) and following cycloplegia (Carkeet *et al*., 2004). Interestingly, cycloplegia appears to have little effect on IOLMaster 500 AL measurements using tropicamide 1% (Sheng *et al*., 2004; Khambhiphant *et al*., 2015) or cyclopentolate HCl 1% (Cheung *et al*., 2009; Arici *et al*., 2014), which is also the case with the IOLMaster 700 after instillation of tropicamide 1% (Momeni-Moghaddam et al., 2019). IOLMaster 500 ACD measurements are affected by cycloplegia with

shallower readings reported prior to, compared to after instillation of the drug, with mean differences of between 0.05 mm (SD ± 0.03) (Cheung *et al*., 2009) and 0.15 mm (SD ± 0.10) (Arici *et al*., 2014) using cyclopentolate HCl 1%, and 0.11 mm with tropicamide 1% (Khambhiphant *et al*., 2015).

Unsurprisingly, results from non-cycloplegic autorefraction are prone to inaccuracies, particularly in young hyperopes due to an active accommodative response (Sankaridurg *et al*., 2017). While refraction undertaken under cycloplegia will yield more accurate results, in the context of tracking longitudinal refractive error changes for research, it is prudent to evaluate both the repeatability of autorefraction and the time course of cycloplegia upon the outcome measure.

The repeatability of autorefraction using the Grand Seiko WAM-5500, 30 minutes after the instillation of tropicamide 1% in a young, adult myopic cohort demonstrated a mean difference between visits of 0.02 D (SD ± 0.11) and LoA of ± 0.21 D (Moore and Bentsen, 2014). Similarly, the repeatability of autorefraction using the Shin-Nippon SRW-5000, in a mixed refractive cohort of children aged 4 to 8 years after the instillation of cyclopentolate HCl 1% has been reported as a mean difference of 0.01 D (SD ± 0.35) with LoA of ± 0.35 D (Chat and Edwards, 2001).

Measures of cycloplegic refraction are typically taken at 30 minutes after the instillation of the drug (Chat and Edwards, 2001; Moore and Bentsen, 2014;) as this has been shown to be the point at which maximum cycloplegia is reached in most children (Laojaroenwanit *et al*., 2016), although this does vary according to iris colour (Manny *et al*., 1993). Regardless of iris colour, the time course for pupil dilation is not the same as the time course for cycloplegia. Some report that maximal cycloplegia is not reached until 90 minutes after instillation of cyclopentolate HCl 1% (Kyei *et al*., 2017). Others suggest that in hyperopes, maximum refractive power is found at 50 to 70 minutes after instillation, although this can be accelerated

by around ten minutes by using a topical anaesthetic prior to the cycloplegic (Xiaoming *et al*., 2011). Nevertheless, the difference in autorefraction taken after instillation of cyclopentolate HCl 1% in emmetropic and hyperopic children at 30 and 60 minutes, respectively, has been reported as being just 0.06 D (SD ± 0.28), with marginally more hyperopia measured at the latter timepoint (Mutti *et al*., 1994). In hyperopes with brown irides, it has been proposed that two drops of cyclopentolate HCl 1% instilled 10 minutes apart should be used to achieve a deeper level of cycloplegia than a single dose (Mohan and Sharma, 2011). In a predominantly hyperopic cohort, others have reported that a single drop of cyclopentolate HCl 1% appears to be sufficient and results in fewer side effects than a multidose approach (Bagheri *et al*., 2007).

Within refractive error modulation studies, measures are typically taken following a specified time period after the instillation of a cycloplegic agent (Anstice and Phillips, 2011; Walline *et al*., 2013; Chamberlain *et al*., 2019a, although others use different criteria for establishing if adequate cycloplegia has been achieved. For instance, some use pupil diameter and absence of a light reflex as marker (Negrel *et al*., 2000), whereas others use measures of accommodative amplitude (Logan *et al*., 2011; Lam *et al*., 2019).

While it is desirable to take measurements in strict accordance with the protocol, the reality, particularly with younger participants, is that there can often be minor departures from the intended plan. For instance, a participant may have measurements taken at precisely 30 minutes after the instillation of the cycloplegic on the first visit, yet unexpected circumstances can mean that assessment takes place several minutes before or after the desired timepoint on a subsequent visit.

Taking all of the above into account, it is useful to confirm the differences that arise in pre-cycloplegic versus post-cycloplegic measures of AL in a mixed refractive cohort and also to determine if there is any short-term variability in these parameters. In addition, being able to elucidate the changes that occur in post-cycloplegic objective refraction across discrete time

intervals on the same visit, along with an assessment of repeatability across visits, provides helpful insight when designing refractive error modulation studies.

5.2 Objective

The purpose of this pilot study was to establish the variation in measures of post-cycloplegic refraction at discrete time intervals and changes to AL measures before and after cycloplegic refraction. The aim was to establish if there was variability in these measures taken at two separate visits across an interval of 1 to 2 weeks.

5.3 Methods

Sample size calculation indicated that 24 participants would be required to achieve 80% power for an effect size of 0.25 at a significance level of 5% using a repeated measures ANOVA design (G*Power 3.1, Franz Faul, Universität Kiel, Germany). The aim was to recruit 28 participants to allow for an attrition rate of 20%. Suitable candidates were enrolled by displaying notices at the research venues. Potential participants were also sourced through a database search at the research venues to identify individuals that met the inclusion criteria.

Prior to commencing the research, ethical approval was obtained from Aston University's Research Ethics Committees (see Appendix 9) with the study designed to follow the tenets of the Declaration of Helsinki. Each participant was given detailed information regarding the nature of the study, both verbally and in written form; this allowed informed consent and assent to take place prior to participation. The participants were required to complete a short questionnaire to ensure they met the inclusion criteria (see Appendix 10).

Inclusion criteria were as follows:

- Aged between 8 and < 31 years-of-age
- Parents must have read, understood and signed the informed consent form where appropriate (see Appendix 11)

- Participants must have read, understood and signed the consent or assent form as appropriate (see Appendix 12 and 13)
- Be in good general health

Exclusion criteria were as follows:

- Current use of systemic medication that could affect focusing ability
- Known ocular or systemic disease
- Participants who were not able to provide informed consent without the aid of an interpreter due to lack of funding available for the provision of interpreter facilities.

Participants were required to attend for two visits taking place within 1 to 2 weeks of each other. A summary of the procedures conducted at each visit are detailed below.

Visit 1

- Unaided DV at 6 m (LogMAR)
- DVA at 6 m (LogMAR)
- Slit lamp examination
- IOPs
- Pre-cycloplegic AL
- Post-cycloplegic autorefraction at 25, 30, 35 and 40 minutes, following instillation of 1 drop of cyclopentolate HCl 1% in minim form (Bausch + Lomb, Kingston upon Thames, UK) in each eye
- Post-cycloplegic AL at 30 minutes
- Post-cycloplegic ACD at 30 minutes.

Visit 2

- Unaided DV at 6 m (LogMAR)

- DVA at 6 m (LogMAR)
- Slit lamp examination
- IOPs
- Pre-cycloplegic AL
- Post-cycloplegic autorefraction at 25, 30, 35 and 40 minutes, following instillation of 1 drop of cyclopentolate HCl 1% in minim form (Bausch + Lomb, Kingston upon Thames, UK) in each eye
- Post-cycloplegic AL at 30 minutes
- Post-cycloplegic ACD at 30 minutes.

5.4 Statistical analysis

All data were analysed using the commercially available software, SPSS, *v*. 25, IBM, New York, U.S.A. (Armstrong et al, 2011; Armstrong et al., 2002). Data were examined with t-tests or repeated measures ANOVA with Bonferroni correction applied, as indicated, with a significance level of $\alpha < 0.05$ used throughout.

5.5 Results

Primary outcome measures (see 5.5.1) were changes in post-cycloplegic MSE refractive error over discrete time intervals at each visit and between the two visits, along with differences in pre- and post-cycloplegic AL measures on and between both visits. Primary outcome measures were the same for the right and left eyes for AL ($F_{1,23} = 0.453$, $P = 0.508$) and post-cycloplegic refraction ($F_{1,23} = 0.754$, $P = 0.394$). As such, data presented here is for the right eye only (Armstrong, 2013).

All 24 participants that were recruited completed the study and comprised of 18 females and 6 males with an age range at baseline of 12.58-29.08 years (mean 19.04 SD 5.66 years); these

data were normally distributed (Kolmogorov-Smirnov, Z = 0.215, P = 0.05). The refractive range was -3.51 D to +5.91 D (mean 2.43 D SD 3.08).

5.5.1 Primary outcome measures

5.5.1.1 AL

Analysis showed that AL measures were the same prior to cycloplegia compared to 30 minutes after instillation of cyclopentolate HCl 1% ($F_{(1, 23)} = 1.231$, P = 0.279). Measures of AL did not change across the two visits ($F_{(1, 23)} = 0.351$, P = 0.559) under pre- or post-cycloplegic conditions ($F_{(1, 23)} = 0.437$, P = 0.515) (see Table 5.1). Observed power was 9.7% and partial η^2 was 0.019.

	AL (mm) (n = 24)	
Timepoint	Pre-cycloplegic	Post-cycloplegic
Visit 1	22.42 ± 0.26	22.42 ± 0.26
Visit 2	22.42 ± 0.26	22.42 ± 0.26

Table 5.1 AL before and 30 minutes after instillation of cyclopentolate HCl 1% at each visit (mean ± SEM)

For pre-cycloplegic AL, the mean difference between Visit 1 and Visit 2 was 0.004 mm SD ± 0.01 (t-test: t = 1.366, df = 23, P = 0.185) with 95% LoA of ± 0.026 mm (see Figure 5.1).

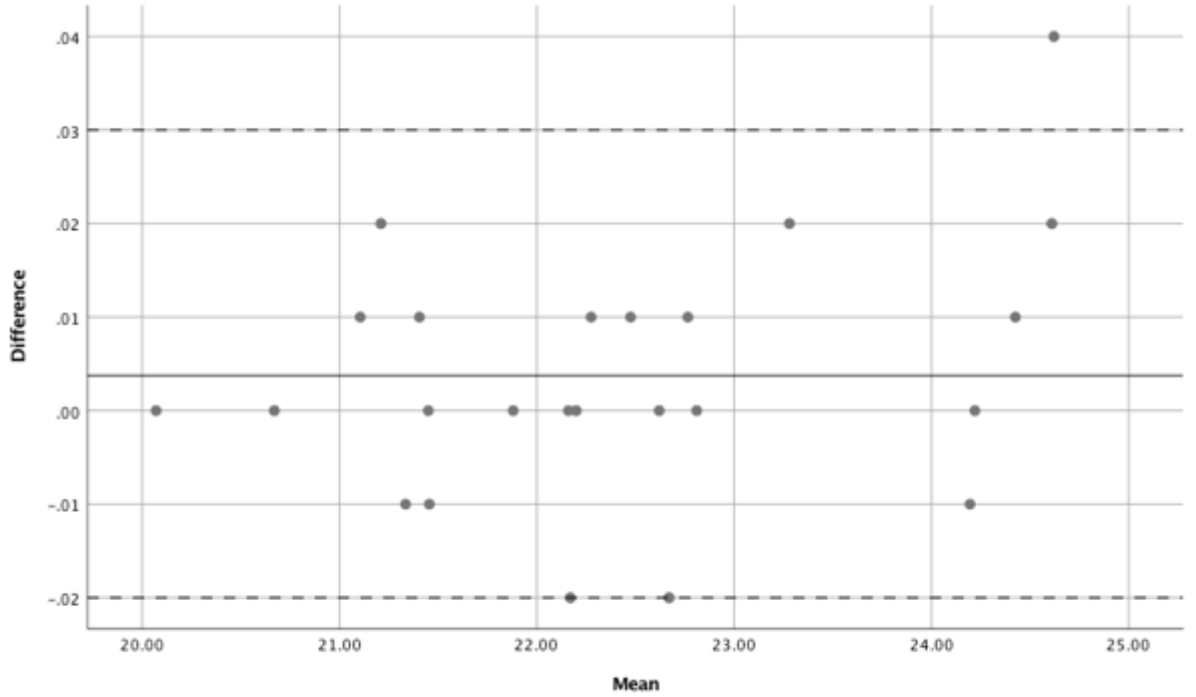

Figure 5.1 Difference *versus* the mean plot for pre-cycloplegic AL at Visits 1 and 2. 95% LoA enclosed by dashed lines. Mean difference indicated by solid line

For post-cycloplegic AL, the mean difference between Visit 1 and Visit 2 was 0.000 mm SD ± 0.013 (t-test: t = 0.000, df = 23, P = 1.000) with 95% LoA of ± 0.025 mm (see Figure 5.2).

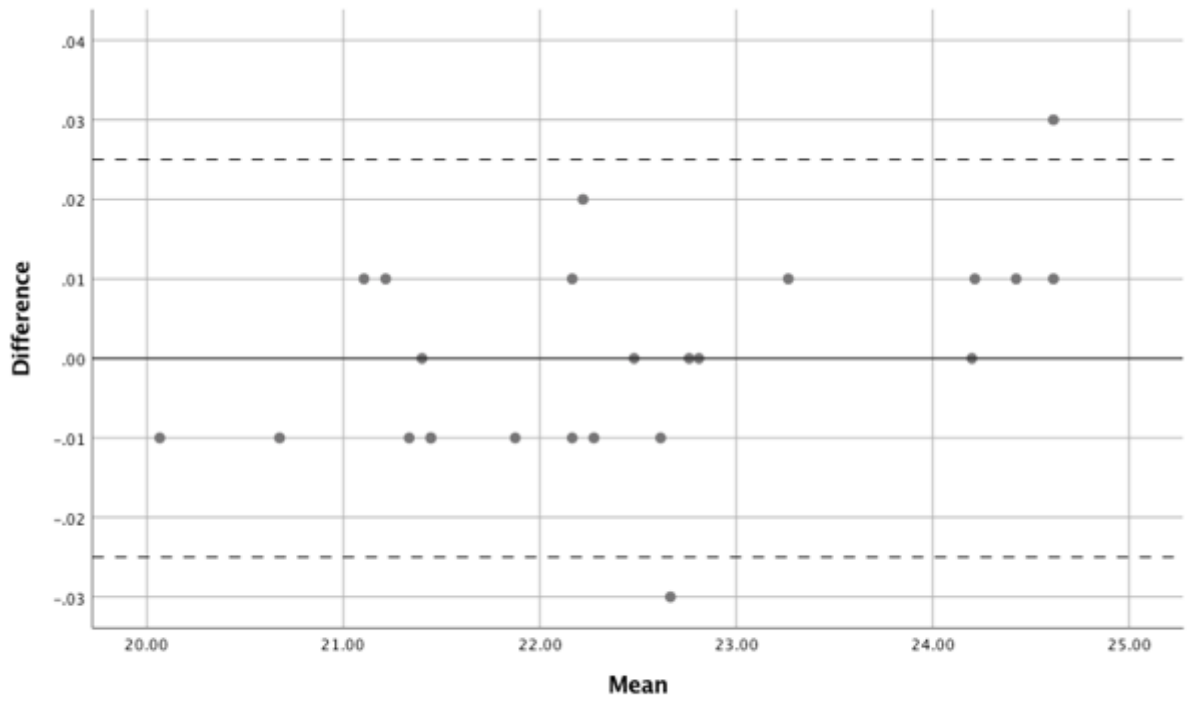

Figure 5.2 Difference *versus* the mean plot for post-cycloplegic AL at Visits 1 and 2. 95% LoA enclosed by dashed lines. Mean difference indicated by solid line

5.5.1.2 Post-cycloplegic refractive error

Analysis for the main effects revealed that post-cycloplegic MSE refractive error did not change over discrete timepoints following cycloplegia ($F_{(1, 23)} = 0.392$, $P = 0.759$). Measures did not change between visits ($F_{(1, 23)} = 0.121$, $P = 0.731$) with no interaction between factors ($F_{(1, 23)} = 0.362$, $P = 0.781$). Observed power was 11.8% and partial η^2 was 0.016.

Pairwise comparisons showed that during the first visit, post-cycloplegic MSE refractive error was the same at 25 ($P = 1.000$), 30 ($P = 1.000$) 35 ($P = 1.000$) and 40 minutes ($P = 1.000$) after instillation of cyclopentolate HCl 1%; this was also the case during the second visit at 25 ($P = 1.000$), 30 ($P = 1.000$) 35 ($P = 1.000$) and 40 minutes ($P = 1.000$), respectively (see Figure 5.3 and Table 5.2).

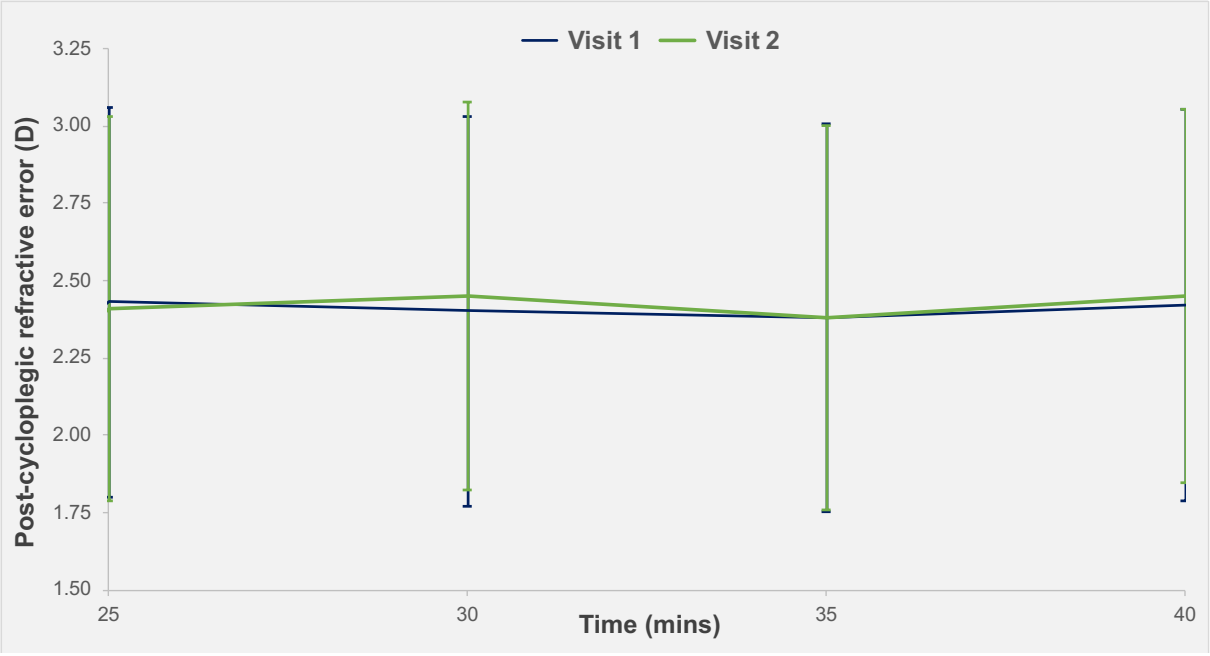

Figure 5.3 Post-cycloplegic MSE refractive error at discrete timepoints after instillation of cyclopentolate HCl 1% at each visit (mean ± SEM)

	Refractive error (D) (n = 24)			
Timepoint	25 mins	30 mins	35 mins	40 mins
Visit 1	2.43 ± 0.63	2.40 ± 0.63	2.38 ± 0.63	2.42 ± 0.63
Visit 2	2.41 ± 0.62	2.45 ± 0.62	2.38 ± 0.62	2.45 ± 0.61

Table 5.2 Post-cycloplegic MSE refractive error at discrete timepoints after instillation of cyclopentolate HCl 1% at each visit (mean ± SEM)

5.5.2 Secondary outcome measures

5.5.2.1 Unaided DV

Unaided DV did not change between Visit 1 and Visit 2 with a mean difference of -0.003 LogMAR SD ± 0.06 (t-test: t = -0.199, df = 23, P = 0.844) (see Table 5.3) with 95% LoA of ± 0.12 LogMAR (see Figure 5.4). Linear regression analysis indicated a level of bias between visits (t = -2.338, P = 0.029).

Timepoint	**DV** (LogMAR) (n = 24)
Visit 1	0.25 ± 0.06
Visit 2	0.25 ± 0.07

Table 5.3 Unaided DV at 6 m at each visit (mean ± SEM)

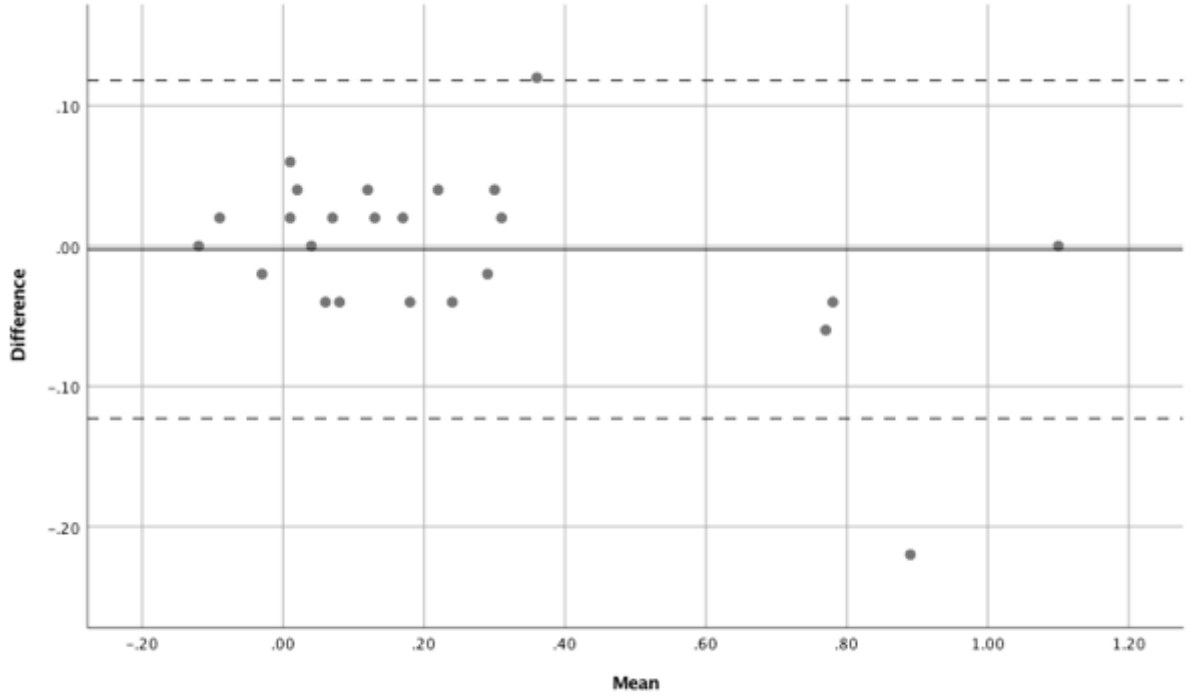

Figure 5.4 Difference *versus* the mean plot for unaided vision at Visits 1 and 2. 95% LoA enclosed by dashed lines. Mean difference indicated by solid line

5.5.2.2 DVA

DVA was unchanged between Visit 1 and Visit 2 with a mean difference of 0.014 LogMAR SD ± 0.06 (t-test: t = 1.204, df = 23, P = 0.241) (see Table 5.4) with 95% LoA of ± 0.11 LogMAR (see Figure 5.5). Linear regression analysis confirmed a level of agreement between visits (t = -1.199, P = 0.243).

Timepoint	**DVA** (LogMAR) (n = 24)
Visit 1	-0.03 ± 0.02
Visit 2	-0.04 ± 0.02

Table 5.4 DVA at 6 m at each visit (mean ± SEM)

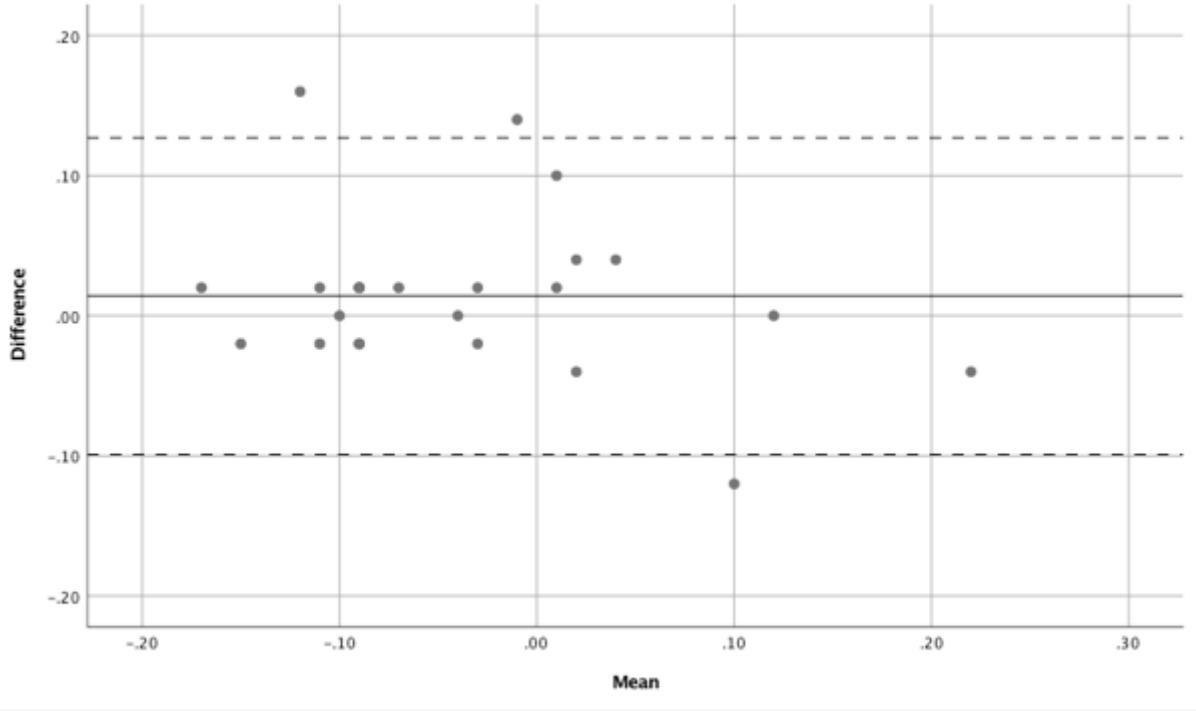

Figure 5.5 Difference *versus* the mean plot for DVA at Visits 1 and 2. 95% LoA enclosed by dashed lines. Mean difference indicated by solid line

5.5.2.3 ACD

ACD did not change between Visit 1 and Visit 2 with a mean difference of 0.002 mm SD ± 0.05 (t-test: t = 0.226, df = 23, P = 0.823) (see Table 5.5) with 95% LoA of ± 0.09 mm (see Figure 5.6). Linear regression analysis confirmed a level of agreement between visits (t = -0.574, P = 0.571).

Timepoint	**ACD** (mm) (n = 24)
Visit 1	3.53 ± 0.06
Visit 2	3.53 ± 0.06

Table 5.5 ACD at each visit (mean ± SEM)

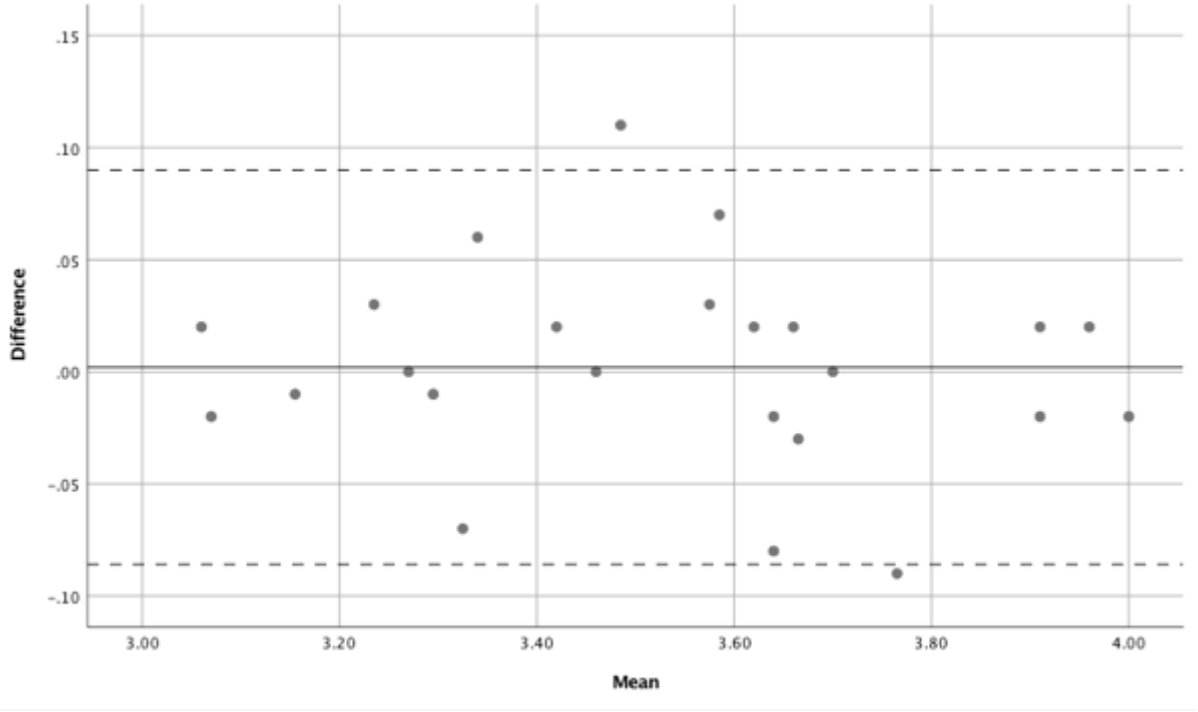

Figure 5.6 Difference *versus* the mean plot for post-cycloplegic ACD at Visits 1 and 2. 95% LoA enclosed by dashed lines. Mean difference indicated by solid line

5.6 Discussion

This pilot study offers useful insight into the influence of cycloplegia on AL and refractive error. These key ocular parameters are typically the primary outcomes in refractive error modulation research, so it is important to understand the effect of cycloplegia on these measures. The study also provides data on the repeatability of the ocular parameters outlined above; this is valuable as it allows researchers to place any changes that have occurred over time, for example, to AL, in the context of variability that may arise naturally across sessions in studies of this type.

In terms of AL measures in this study, there are two important aspects to consider: firstly, the repeatability of AL measures under both non-cycloplegic and cycloplegic conditions; secondly, to understand the impact of a cycloplegic agent on AL. These insights allow researchers to review options when designing refractive error modulation experimental paradigms. For instance, in Chapters 3 and 4, participants had axial growth monitored under pre-cycloplegic conditions over a 3-year period at 6-monthly intervals, that is to say, on 7 visits in total. In the same trials, post-cycloplegic refractive error was evaluated on 5 visits over the same 3-year interval. In other words, a cycloplegic agent was only used on 5 out of the 7 visits. In the present study, measures of AL in a young, mixed refractive cohort were the same under non-cycloplegic and cycloplegic conditions across two separate visits. The outcome here is reassuring as it gives researchers the confidence to design refractive error modulation studies, in line with the paradigm adopted for Chapters 3 and 4, without necessarily having to specify that a cycloplegic agent is required in order to track longitudinal axial growth. There are several benefits that arise from this finding: recruitment of participants may become easier, particularly with young children if cycloplegia is either not required, or if the requirement can be removed at certain data collection points; the burden of cycloplegia for participants can be removed or frequency reduced in study designs; researchers can take the opportunity to investigate other secondary outcome measures under non-cycloplegic conditions at intervals where a cycloplegic agent is not required, for example, peripheral refraction with CLs *in situ* under natural a refractive state (see Chapters 3 and 4).

The present study also investigated both the repeatability of cycloplegic refraction in a young, mixed refractive cohort and the impact of duration of drug exposure at discrete time intervals. In terms of repeatability, as with AL measures described above, it is essential to understand natural variability in cycloplegic refraction that can arise between measurement sessions so that any reported changes are attributed confidently to a particular intervention. In addition, it is important to understand the effect that variability in the duration of drug exposure can have on the outcome measures; in the author's experience, it is not unusual for participants to

unintentionally return later than specified time following instillation of the cycloplegic. For example, the participant or a younger sibling may request a comfort break prior to resuming data collection, resulting in measures being taken several minutes after the intended timepoint. As such, it is helpful to elucidate the potential impact of these discrete time deviations. It is reassuring to note that the results from the present study show that measures of refractive error taken at four time points across a 15-minute window do not differ significantly and are repeatable across two measurement sessions.

In terms of secondary outcome measures, this study has shown that in line with previous work, measures of unaided DV and DVA (Raasch *et al*., 1998; Siderov and Tiu, 1999), and ACD (Lam *et al*., 2001; Sheng *et al*., 2004) are repeatable.

In summary, the results of this study have shown that AL does not change significantly when comparing measures taken before and after the introduction of a cycloplegic agent in a young, mixed refractive cohort. The other main outcome from this study offers reassurance to researchers that objective measures of cycloplegic refraction are repeatable and do not vary significantly across discrete time intervals. Further work could look to explore objective measures of cycloplegic refraction at a greater spread of timepoints to establish if this key outcome measure can be reliably taken within a shorter window to increase the efficiency of data collection for the benefit of participants and investigators. It would be helpful if this pilot work could be expanded upon with a larger sample to achieve statistical power, and given the effect size determined in the present work, this would require 190 participants.

6.0 General discussion

The overarching conclusion from this body of work provides evidence to support the original hypothesis and offers a clinically accessible mechanism to reduce the lifelong impact of hyperopia. But there is more to do. Indeed, it is important to recognise that the clinical trials outlined here are a starting point in an area of research that, against the backdrop of the myopia epidemic, has thus far been neglected.

The primary outcome measures outlined in Chapter 3 demonstrate the ability to accelerate axial growth in isohyperopes. Two-year axial growth rates of 0.17 mm *versus* 0.06 mm in the intervention and control groups, respectively, shows promise. In terms of the second primary outcome measure, post-cycloplegic error, while the decrease in hyperopia did not reach statistical significance, the overall trend was in the desired direction and an extension of the work is required with a larger sample size to achieve sufficient power. Furthermore, a larger sample size would permit further statistical analysis, such as multiple linear regression, to help identify factors that may predict potential responders to the types of intervention outlined in the present work. It is also worth noting the effects of 'optical dampening' and the reduction in the refraction: AL ratio seen in larger myopic eyes (Cruickshank and Logan, 2018) and how this may translate into a greater refractive impact for those with smaller globes, namely hyperopes. In other words, an increase in AL in a small, hyperopic eye would be expected to result in a larger refractive change than an equivalent AL change in a larger eye. Once again, this could be elucidated with a sufficiently large dataset.

A deeper delve into the raw data clearly shows that while the majority of children respond to the intervention, there appears to be others that could be regarded as non-responders, where growth rates follow a natural time course. Interestingly, the two best responders were almost 3 years younger and had a baseline refraction ~ +2.00 D lower than the two worst responders (see Appendix 14). While a trend cannot be established from this small-scale observation, it is

intriguing, and the relevance of age and refractive error at baseline should be explored in future work.

Establishing proof of concept and taking into account lessons learnt throughout the experimental chapters has created a platform to develop the efficacy of this approach. In the first instance, it would be useful to assess the impact of earlier intervention. While the entry point for participants in the present study was 8 years of age, the mean age was > 11 years. Nevertheless, it is worth stressing that recruitment of hyperopes within primary care and research settings is challenging, particularly within a younger age group. In the absence of amblyopia or symptoms, low to moderate hyperopes are likely to 'pass' rudimentary vision screening at school (O'Donoghue *et al*., 2012) and may not present for routine assessment within primary care optometry. On the other hand, strabismic and / or amblyopic hyperopes are usually diverted to secondary care and not discharged to primary care until beyond the age of 7 years. Taking the above into account, two points need to be addressed, at least in the UK. Firstly, as with dental care, it is essential to place the visual welfare of young children on the healthcare checklist of parents. A timely visit to primary care optometry would allow for pre-school detection of latent hyperopia, amblyopia and anisometropia, creating the best opportunity for intervention. Although, as a sidenote, it seems there is still some work to do within the profession itself to educate practitioners on taking an evidence-based approach to inform clinical decisions when using cycloplegia during paediatric examinations (Doyle *et al*., 2019). Secondly, there is a pressing need for research collaboration with Hospital Eye Service colleagues, once again, to maximise the visual prognosis for these children at the earliest possible stage.

Additional opportunities to expand upon refractive error modulation in children with hyperopia could be through nuanced optical approaches based upon the mechanism established in Chapter 3. In the present study, a single dose approach was taken using a 2.00 D add in an 'off-the-shelf' design intended for presbyopic correction. Due to minimal axial growth typically

seen in hyperopes, '*…they really need to have a good kick in the pants to reactivate their long dormant growth...*' (Dr Thomas Aller, California, US, personal communication, 4 September 2020). In this context, a 'good kick' refers to using custom-designed MF CLs, in the smallest sized central zone and the highest add power that the child will tolerate; this approach is not unreasonable given that myopic defocus, at least in chicks, seems to have greater potency than hyperopic defocus (Zhu *et al*., 2005; Zhu, 2013). Furthermore, customising the design to ensure sufficient RPHD in all four quadrants on an individual basis may also yield better results.

There remains, as with myopes, conjecture as to whether the signal for accelerated growth observed in this cohort was due to the imposition of RPHD, the effect of the intervention upon accommodative lag, or both. From a clinician's standpoint, and certainly from the patient's perspective, does it really matter? Nevertheless, from a research stance, this question requires answering, at the very least to satisfy curiosity, but more importantly to hone future approaches in this area.

While the results in Chapter 3 bring optimism and a firm foundation on which to build, the results for anisohyperopes in Chapter 4 are an intriguing contrast to their isohyperopic counterparts. In view of the fact that as little as 0.50 D of anisometropia is enough to disrupt emmetropisation (Flitcroft *et al*., 2020) and given that participants in the present trial had a minimum baseline interocular difference in refractive error of >1.00 D, they were arguably faced with an uphill battle to achieve the intended outcome, particular at the age inclusion criteria specified in the study. Of course, the points raised previously in relation to early intervention are equally valid here, but perhaps also the definition of anisometropia ought to be softened and interocular differences of >0.50 D should be regarded as abnormal enough to warrant intervention. Once again, as with isohyperopes, anisohyperopes may also benefit from a 'good kick.'

As alluded to in Chapter 4 (see Section 4.6), for anisohyperopes specifically, a more aggressive approach could be taken with the *least* hyperopic eye. The rationale for this is that in the present study, it was the 'better' eye that appeared to display a more atypical growth rate than its fellow. Could the 'better' eye actually be regarded as the abnormal one of the pair in the case of anisohyperopes? With this in mind, the eye closer to emmetropia could be treated in the same way as a progressing myope by imposing relative peripheral *myopic* defocus (RPMD) to slow down axial growth. Of course, this does not preclude the opportunity to simultaneously impose RPHD in the fellow eye to maximise the chances of narrowing the interocular difference in refractive error. Building upon this concept, even a pharmacological strategy could be employed in those with anisohyperopia by trying to slow down growth in the eye closest to emmetropia. Indeed, there is precedent for this in the context of myopic anisometropia where atropine has been used successfully to slow down axial growth only in the eye with the highest refractive error (Lixia *et al*., 2013).

Regardless of the effect of RPHD on axial growth modulation, or lack thereof, in anisohyperopes, it is worth emphasising the point from Chapter 1 (see Section 1.3.3) in relation to the advantages of CL wear for these individuals. Certainly, practitioners should at least be mindful that correction of anisometropia with this form of correction instead of spectacles facilitates the potential for normal binocular vision (Winn *et al*., 1986; Romano and von Noorden, 1999) and can deliver improvements to VA.

Outside of CL modalities, novel spectacle lens designs for both aniso- and isohyperopes remains an unexplored area of research. Could lessons be learnt from existing spectacle lens designs for myopia such as the DIMS lens? A central optic zone to provide full refractive correction surrounded by multiple segments to deliver constant hyperopic of defocus of -3.50 D perhaps?

In addition to the experimental chapters relating to refractive error modulation, the pilot study summarised in Chapter 5 offers reassurance to practising clinicians and researchers that the typical approach to collection of key data in this field is robust. In particular, post-cycloplegic measures across a broad range of refractive errors are comparable at 25 minutes through to 40 minutes, which provides scope for leeway when making assessments in the clinic or lab. In addition, it seems that AL measures are repeatable and comparable under both cycloplegic and non-cycloplegic conditions.

In summary, it is hoped that by demonstrating the ability to modulate refractive error in isohyperopes, this will generate sufficient intrigue to build upon this work. There is much to do. For instance, it would be desirable to undertake a multicentre randomised control trial with customised MF CL designs, to explore the potential for novel spectacle lens designs, and to consider a different approach to the management of anisohyperopes with scope to use pharmacological agents.

References

Abrahamsson M and Sjöstrand J (1996) Natural history of infantile anisometropia. *Br J Ophthalmol* 80:860-863

Abrahamsson M, Fabian G and Sjostrand J (1990) A longitudinal study of a population based sample of astigmatic children. II. The changeability of anisometropia. *Acta Ophthalmol (Copenh)* 68: 435–440

Adler D and Millodot M (2006) The possible effect of under correction on myopic progression in children. *Clin Exp Optom* 89:315-21

Aleman A and Schaeffel F (2018) Lag of accommodation does not predict changes in eye growth in chickens. *Vision Res* 149:77-85

Aller TA, Liu M and Wildsoet CF (2016) Myopia control with bifocal contact lenses: a randomized clinical trial. *Optom Vis Sci* 93(4):344-52

Anstice NS and Phillips JR (2011) Effect of dual-focus soft contact lens wear on axial myopia progression in children. *Ophthalmology* 118:1152-61

Arici C, Turk A, Ceylan OM, and Kola M (2014) The Effect of Topical 1% Cyclopentolate on IOLMaster Biometry. *Optom Vis Sci* 91:1343-1347

Armstrong RA, Eperjesi F and Gilmartin B (2002) The application of analysis of variance (ANOVA) to different experimental designs in optometry. *Ophthalmic Physiol Opt* 22:248-256

Armstrong RA, Davies LN, Dunne MCM and Gilmartin B (2011) Statistical guidelines for clinical studies of human vision. *Ophthalmic Physiol Opt* 31:123-136

Armstrong RA (2013) Statistical guidelines for the analysis of data obtained from one or both eyes. *Ophthalmic Physiol Opt* 33:7-14

Artal P, Guirao A, Berrio E and Williams DR (2001) Compensation of corneal aberrations by the internal optics in the human eye. *J Vis* 1:1-8

Ashby RS and Schaeffel F (2010) The effect of bright light on lens compensation in chicks. *Invest Ophthalmol Vis Sci* 51:5247-5253

Ashby R, Ohlendorf A and Schaeffel F (2009) The effect of ambient illuminance on the development of deprivation myopia in chicks. *Invest Ophthalmol Vis Sci* 50:5348-5354

Atchison DA, Li SM, Li H, Li SY, Liu LR, Kang MT, *et al* (2015) Relative peripheral hyperopia does not predict development and progression of myopia in children. *Invest Ophthalmol Vis Sci* 56:6162-6170

Atchison DA and Charman WN (2011) Can partial coherence interferometry be used to determine retinal shape? *Optom Vis Sci* 88:601-607

Atkinson J, Anker S, Bobier W, Braddick O, Durden K, Nardini M et al (2000) Normal emmetropization in infants with spectacle correction for hyperopia. *Invest Ophthalmol Vis Sci* 41:3726-3731

Atkinson J, Braddick O, Nardini M and Anker S (2007) Infant hyperopia: Detection, distribution, changes and correlates-outcomes from the Cambridge infant screening programs. *Optom Vis Sci* 84:84-96

Atchison DA, Pritchard N, Schmid KL, Scott DH, Jones CE and Pope JM (2005) Shape of the retinal surface in emmetropia and myopia. *Invest Ophthalmol Vis Sci* 46:2698-2707

Atchison DA and Rosén R (2016) The possible role of peripheral refraction in development of myopia. *Optom Vis Sci* 93:1042-1044

Atchison DA, Schmid KL, Pritchard N (2006) Neural and optical limits to visual performance in myopia. *Vision Res* 46:3707-3722

Atyeiza A and Davis H (2019) The Effects of Anisometropic Amblyopia on the FNS and TNO Stereotest Thresholds in Four- to Eight-Year-Olds. *Brit Irish Orthop J* 15(1):72-81

Bailey IL and Lovie JE (1976) New design principles for visual acuity letter charts. *Am J Optom Physiol Opt* 53:740-745

Bagheri A, Givrad S, Yazdani S and Reza Mohebbi M (2007) Optimal Dosage of Cyclopentolate 1% for Complete Cycloplegia: A Randomized Clinical Trial. *Eur J Ophthalmol* 17(3):294-300

Bandello F, Tavola A, Pierro L, Modorati G, Azzolini C and Brancato R (1998) Axial length and refraction in retinal vein occlusions. *Ophthalmologica* 212:133-5

Barrett BT, Bradley A and Candy TR (2013) The Relationship between Anisometropia and Amblyopia. *Prog Retin Eye Res* 23:120-158

Beasley IG, Laughton DS, Coldrick BJ, Drew TE, Sallah M and Davies LN (2013) Does Rebound Tonometry Probe Misalignment Modify Intraocular Pressure Measurements in Human Eyes? *J Ophthalmol* 791084

Beasley IG, Davies LN and Logan NL (2018) Effect of Peripheral Defocus on Axial Eye Growth and Modulation of Refractive Error in Hyperopes: Protocol for a Nonrandomized Clinical Trial. *JMIR Res Protoc* 7(9):e173

Benavente-Pérez A, Nour A and Troilo D (2012a) The effect of simultaneous negative and positive defocus on eye growth and development of refractive state in marmosets. *Invest Ophthalmol Vis Sci* 53:6479-6487

Benavente-Pérez A, Nour A and Troilo D (2012b) Peripheral refraction as a predictor for induced changes in vitreous chamber growth rates in marmosets. *Invest Ophthalmol Vis Sci* 53:4662

Benavente-Pérez A, Nour A and Troilo D (2014) Asymmetries in peripheral refraction in marmosets change with emmetropization and induced eye growth. *Invest Ophthalmol Vis Sci* 55:2731

Benavente-Pérez A, Nour A and Troilo D (2014) Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. *Invest Ophthalmol Vis Sci* 55:6765-6773

Benavente-Pérez A, Nour A and Troilo D (2016) The role of peripheral refraction in emmetropization: evidence from marmoset studies. *Eye Vision* 3:1-11

Berntsen DA, Sinnott LT, Mutti DO and Zadnik K (2012) A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. *Invest Ophthalmol Vis Sci* 53:640-649

Borchert M, Tarczy-Hornoch K, Cotter SA, Liu N, Azen SP, Varma R, *et al* (2010) Anisometropia in Hispanic and African American infants and young children the multi-ethnic pediatric eye disease study. *Ophthalmology* 117:148-153.e1

Breslin KMM, O'Donoghue L and Saunders KJ (2013) A prospective study of spherical refractive error and ocular components among Northern Irish schoolchildren (The NICER Study). *Invest Ophthalmol Vis Sci* 54:4843-4850

Brookman KE (1983) Ocular Accommodation in Human Infants. *Am J Optom Physiol Opt* 60:91–99

Brunette I, Bueno JM, Parent M, Hamam H and Simonet P (2003) Monochromatic aberrations as a function of age, from childhood to advanced age. *Invest Ophthalmol Vis Sci* 44:5438-5446

Bullimore MA, Fusaro RE and Adams CW (1998) The Repeatability of Automated and Clinician Refraction. *Optom Vis Sci* 75(8):617-622

Bullimore MA (2017) The Safety of Soft Contact Lenses in Children. Optom Vis Sci 94:638-646

Burns DH, Allen PM, Edgar DF and Evans B (2020) Sources of error in clinical measurement of the amplitude of accommodation *J Optom* 13:3-14

Burtolo C, Ciurlo C, Polizzi A, Lantier PB and Calabria G (2002) Echobiometric study of ocular growth in patients with amblyopia. *J Pediatr Ophthalmol Strabismus* 39:209-214

Carkeet A, Saw SM, Gazzard G, Tang W and Tan DTH (2004) Repeatability of IOLMaster biometry in children. *Optom Vis Sci* 81(11):829-834
Carl Zeiss Meditec. IOLMaster Practical Operation Guide

Candy TR and Bharadwaj SR (2007) The stability of steady state accommodation in human infants. *J Vis* 7(4):1–16

Carkeet A, Luo HD, Tong L, Saw MS and Tan DTH (2002) Refractive error and monochromatic aberrations in Singaporean children. *Vision Res* 42:1809-1824

Casson RJ, Baker M, Edussuriya K, Senaratne T, Selva D and Sennanayake S (2009) Prevalence and determinants of angle closure in central Sri Lanka: the Kandy Eye Study. *Ophthalmology* 116:1444-1449

Castejón-Mochón JF, López-Gil N, Benito A and Artal P (2002) Ocular wave-front aberration statistics in a normal young population. Vision Res 42:1611-1617

Chakraborty R, Ostrin A, Benavente-Perez A and Verkicharla PK (2020) Optical mechanisms regulating emmetropisation and refractive errors: evidence from animal models. *Clin Exp Optom* 103:55-67

Chakraborty R, Read SA and Collins MJ (2012) Monocular myopic defocus and daily changes in axial length and choroidal thickness of human eyes. *Exp Eye Res* 103:47-54

Chakraborty R, Read SA and Collins MJ (2013) Hyperopic defocus and diurnal changes in human choroid and axial length. *Optom Vis Sci* 90:1187-1198

Chalmers RL, McNally JJ, Chamberlain P and Keay L (2021) Adverse event rates in the retrospective cohort study of safety of paediatric soft contact lens wear: the ReCSS study. *Ophthalmic Physiol Opt* 41:84-92

Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D and Young G (2019a) A 3-year Randomized Trial of MiSight Lenses for Myopia Control. *Optom Vis Sci* 96:556-567

Chamberlain P, Logan N, Jones D, Gonzalez-Meijome J, Saw S-M and Young G (2019b) Clinical evaluation of a dual-focus myopia control 1 day soft contact lens: 5-year results. BCLA Clinical Conference & Exhibition

Chamberlain P, Logan N, Jones D, Gonzalez-Meijome J, Saw S-M and Young G (2020) Clinical evaluation of a dual-focus myopia control 1 day soft contact lens: 6-year results. American Academy of Optometry Annual Meeting)

Charm J and Cho P (2013) High myopia-partial reduction ortho-k: a 2-year randomized study. *Optom Vis Sci* 90:530-539

Charman WN (1991) Wavefront aberration of the eye: a review. *Optom Vis Sci* 68:574-583

Charman WN (1999) Near vision, lags of accommodation and myopia. *Ophthalmic Physiol Opt* 19:126-133

Charman WN (2005) Aberrations and myopia. *Ophthalmic Physiol Opt* 25:285-301

Charman WN and Jennings JAM (1995) Recognition of TNO stereotest figures in the absence of true stereopsis. *Optom Vis Sci* 72(7):535-536

Charman WN and Radhakrishnan H (2010) Peripheral refraction and the development of refractive error: a review. *Ophthalmic Physiol Opt* 30:321–338

Chat SWS and Edwards MH (2001) Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in children. *Ophthalmol Physiol Opt* 21(2):87-100

Chen X, Sankaridurg P, Donovan L, Lin Z, Li L, Martinez A, *et al* (2010) Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res* 50(1):31-5

Chen C, Cheung SW and Cho P (2013) Myopia control using toric orthokeratology (TO-SEE study). *Invest Ophthalmol Vis Sci* 54:6510-6517

Chen S, Zhi Z, Ruan Q, Liu Q, Li F, Wan F, *et al* (2017) Bright light suppresses form-deprivation myopia development with activa- tion of dopamine D1 receptor signaling in the ON pathway in retina. *Invest Ophthalmol Vis Sci* 58:2306-2316

Cheng X, Bradley A, Hong X and Thibos LN (2003) Relationship between refractive error and monochromatic aberrations of the eye. *Optom Vis Sci* 80:43-49

Cheng D, Woo GC, Drobe B and Schmid KL (2014) Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. *JAMA Ophthalmol* 132:258-264

Cheng X, Xu J, Chehab K, Exford J and Brennan N (2016) Soft contact lenses with positive spherical aberration for myopia control. *Optom Vis Sci* 93:353–366

Cheung SW, Chan R, Cheng RCS and Cho P (2009) Effect of cycloplegia on axial length and anterior chamber depth measurements in children. *Clin Exp Optom* 92(6):476-481

Chia A, Dirani M, Chan YH, Gazzard G, Au Eong KG, Selvaraj P, *et al* (2010) Prevalence of amblyopia and strabismus in young Singaporean Chinese children. *Invest Ophthalmol Vis Sci* 51:3411-3417

Cho P and Cheung SW (2012) Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci* 53:7077-7085

Cho P, Cheung SW and Edwards M (2005) The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. *Curr Eye Res* 30:71-80

Choh V, Lew MY, Nadel MW and Wildsoet CF (2006) Effects of inter-changing hyperopic defocus and form deprivation stimuli in normal and optic nerve-sectioned chicks. *Vision Res* 46:1070-1079

Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, *et al* (2006) Atropine for the treatment of childhood myopia. *Ophthalmology* 113: 2285-2291

Chung K, Mohidin N and O'Leary DJ (2002) Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res* 42: 2555-2559

Ciner EB, Kulp MT, Pistilli M, Ying G-S, Maguire M, Candy TR, *et al* ; on behalf of the Vision In Preschoolers - Hyperopia In Preschoolers (VIP-HIP) Study Group (2021) Associations between visual function and magnitude of refractive error for emmetropic to moderately hyperopic 4- and 5-year-old children in the Vision in Preschoolers - Hyperopia in Preschoolers Study. *Ophthalmic Physiol Opt* 41:553–564

Clarke RJ, Coimbra CJ and Alessio ML (1985) Oculomotor areas involved in the parasympathetic control of accommodation and pupil size in the marmoset (Callithrix jacchus). *Braz J Med Biol Res* 18:373-379

Cohen Y, Belkin M, Yehezkel O, Solomon AS and Polat U (2011) Dependency between light intensity and refractive development under light-dark cycles. *Exp Eye Res* 92:40-46

Colburn JD, Morrison DG, Estes RL, Li C, Lu P, Donahue SP (2010) Longitudinal follow-up of hypermetropic children identified during preschool vision screening. *J AAPOS* 14:211-215

Coletta NJ, Marcos S and Troilo D (2010) Ocular wavefront aberrations in the common marmoset Callithrix jacchus: effects of age and refractive error. *Vision Res* 50:2515-2529

Congdon NG, Youlin Q, Quigley H, Hung PT, Wang TH, Ho TC, *et al* (1997) Biometry and primary angle-closure glaucoma among Chinese, white, and black populations. *Ophthalmology* 104:1489-1495

CooperVision https://coopervision.co.uk/practitioner/contact-lenses/biofinitity [Accessed 06/09/2020]

Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator

Group (2011) Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. *Invest Ophthalmol Vis Sci* 52:2749-2757

Cotter SA (2007) Management of childhood hyperopia: a pediatric optometrist's perspective. *Optom Vis Sci* 84:103-109

Cotter SA, Varma R, Tarczy-Hornoch K, McKean-Cowdin R, Lin J, Wen G, *et al* (2011) Risk factors associated with childhood strabismus: the multi-ethnic pediatric eye disease and Baltimore pediatric eye disease studies. *Ophthalmology* 118:2251-2261

Covey M, Sweeney DF, Terry R, Sankaridurg PR and Holden BA (2001) Hypoxic Effects on the Anterior Eye of High-Dk Soft Contact Lens Wearers Are Negligible. *Optom Vis Sci* 78(2):95-99

Crawford K, Terasawa E and Kaufman PL (1989) Reproducible stimulation of ciliary muscle contraction in the cynomolgus monkey via a permanent indwelling midbrain electrode. *Brain Res* 503:265-272

Croft MA, Kaufman PL, Crawford KS, Neider MW, Glasser A and Bito LZ (1998) Accommodation dynamics in aging rhesus monkeys. *Am J Physiol* 275:R1885-R1897

Cruickshank FE & Logan NS (2018) Optical 'dampening' of the refractive error to axial length ratio: implications for outcome measures in myopia control studies. *Ophthalmic Physiol Opt* 38:290-297

Davies LN, Mallen EAH, Wolffsohn JS and Gilmartin B (2003) Clinical Evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR-5100K Autorefractor. *Optom Vis Sci* 80(4):320-324

Davies LN, Bartlett H, Mallen EAH and Wolffsohn JS (2006) Clinical evaluation of rebound tonometer. *Acta Ophthalmol Scand* 84(2):206-209

Davies LN, Mallen EAH (2009) Influence of accommodation and refractive status on the peripheral refractive profile. *Br J Ophthalmol* 93**:**1186-1190

Day M, Gray LS, Seidel D and Strang NC (2009) The relationship between object spatial profile and accommodation microfluctuations in emmetropes and myopes. *J Vis* 9:1-13

de Vries J (1985) Anisometropia in children: analysis of a hospital population. *Br J Ophthalmol* 69:504-507

Del Águila-Carrasco AJ, Marín-Franch I, Bernal-Molina P, Esteve-Taboada JJ, Kruger PB, Montés-Micó, *et al* (2017) Accommodation responds to optical vergence and not defocus blur alone. *Invest Ophthalmol Vis Sci* 58:1758-1763

Deng L, Gwiazda JE (2012) Anisometropia in Children from Infancy to 15 Years. *Invest Ophthalmol Vis Sci* 53: 3782–3787

Diether S and Schaeffel F (1997) Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res* 37:659-668

Diether S and Wildsoet CF (2005) Stimulus requirements for the decoding of myopic and hyperopic defocus under single and competing defocus conditions in the chicken. *Invest Ophthalmol Vis Sci* 46:2242-2252

Dirani M, Shekar SN and Baird PN (2008) Adult-Onset Myopia: The Genes in Myopia (GEM) Twin Study. *Invest Ophthalmol Vis Sci* 49: 3324–3327

Dobson V, Harvey EM, Miller JM and Clifford-Donaldson CE (2008) Anisometropia prevalence in a highly astigmatic school-aged population. *Optom Vis Sci* 85:512-519

Doherty SE, Doyle LA, MCCullogh SJ and Saunders KJ (2019) Comparison of retinoscopy results with and without 1% cyclopentolate in school-aged children. *Ophthalmic Physiol Opt* 39:272-281

Donahue SP (2007) Prescribing spectacles in children: a pediatric ophthalmologist's approach. *Optom Vis Sci* 84:110-114

Doyle LA, McCullough SJ and Saunders KJ (2019) Cycloplegia and spectacle prescribing in children: attitudes of UK optometrists. *Ophthalmic Physiol Opt* 39:148-161

Drobe B and De Saint-André R (1995) The pre-myopic syndrome. *Ophthalmic Physiol Opt* 15:375-378

Edwards MH, Li RW, Lam CS, Lew JKF and Yu BSY (2002) The Hong Kong progressive lens myopia control study: study design and main findings. *Invest Ophthalmol Vis Sci* 43:2852-2858

Ehrlich DL, Braddick OJ, Atkinson J, Anker S, Weeks F, Hartley T, *et al* (1997) Infant emmetropization: longitudinal changes in refraction components from nine to twenty months of age. *Optom Vis Sci* 74(10):822-843

Elliott DB and Hurst MA (1990) Simple Clinical Techniques to Evaluate Visual Function in Patients with Early Cataract. *Optom Vis Sci* 67(11):822-825

Elliott DB, Bullimore MA, Bailey IL (1991) Improving the reliability of the Pelli-Robson contrast sensitivity test. *Clin Vis Sci* 6(6):471-475

Elbaz U, Barkana Y, Gerber Y, Avni I and Zadok D (2007) Comparison of different techniques of anterior chamber depth and keratometric measurements. *Am J Ophthalmol* 143(1):48-53

Farhood QK. Cycloplegic refraction in children with cyclopentolate versus atropine (2012) *J Clin Exp Ophthalmol* 3:239

Fernandes P, Díaz-Rey JA, Queirós A, J. M. Gonzalez- Meijome JM and Jorge J (2005) Comparison of the ICare rebound tonometer with the Goldmann tonometer in a normal population *Ophthalmic Physiol Opt* 25:436-440

Ferrer-Blasco and Madrid-Costa (2011) Stereoacuity with balanced presbyopic contact lenses *Clin Exp Optom* 94(1):76-81

Flanagan SC, Cobice D, Richardson P, Sittlington JJ and Saunders KJ (2020) Elevated melatonin levels found in young myopic adults are not attributable to a shift in circadian phase. *Invest Ophthalmol Vis Sci* 61(8):45

Fledelius HC and Christensen AC (1996) Reappraisal of the human ocular growth curve in fetal life, infancy, and early childhood. *Br J Ophthalmol* 80:918-921

Fledelius HC, Christensen AS and Fledelius C (2014) Juvenile eye growth, when completed? An evaluation based on IOL-Master axial length data, cross-sectional and longitudinal. *Acta Ophthalmol* 92:259-264

Flitcroft DI (2012) The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res* 31:622-660

Flitcroft DI (2013) Is myopia a failure of homeostasis? *Exp Eye Res* 114:16-24

Flitcroft DI (2014) Emmetropisation and the aetiology of refractive errors. *Eye* 28:169-179

Flitcroft I, McCullough S and Saunders K (2020) What can anisometropia tell us about eye growth? *Br J Ophthalmol* 316406

Flom MC and Bedell HE (1985) Identifying amblyopia using associated conditions, acuity, and nonacuity features. *Am J Optom Physiol Opt* 62(3):153-160

Flom MC and Neumaier RW (1966) Prevalence of amblyopia. *Public Health Rep* 81(4):329-341

Flitcroft DI and Morley JW (1996) Accommodation in Binocular Contour Rivalry. *Vision Res* 37(1):121-125

Foulds WS, Barathi VA and Luu CD (2013) Progressive myopia or hyperopia can be induced in chicks and reversed by manipulation of the chromaticity of ambient light. *Invest Ophthalmol Vis Sci* 54:8004-8012

French AN, O'Donoghue L, Morgan IG, Saunders KJ, Mitchell P, Rose KA (2012) Comparison of refraction and ocular biometry in European Caucasian children living in Northern Ireland and Sydney, Australia. *Invest Ophthalmol Vis Sci* 53:4021-4031

Friedman DS, Repka MX, Katz J, Giordano L, Ibironke J, Hawse P, *et al* (2009) Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months the Baltimore Pediatric Eye Disease Study. *Ophthalmology* 116(11):2128-2134

Fulk GW, Cyert LA and Parker DE (2000) A randomized trial of the effect of single-vision vs. bifocal lenses on myopia progression in children with esophoria. *Optom Vis Sci* 77:395-401

Gamlin PD, McDougal DH, Pokorny J, Smith VC, Yau KW and Dacey DM (2007) Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. *Vision Res* 47:946-954

García de la Cera E, Rodríguez G and Marcos S (2006) Longitudinal changes of optical aberrations in normal and form-deprived myopic chick eyes. *Vision Res* 46:579-589

Gawne TJ, Siegwart JT Jr, Ward AH and Norton TT (2017b) The wavelength composition and temporal modulation of ambient lighting strongly affect refractive development in young tree shrews. *Exp Eye Res* 155:75-84

Gawne TJ, Ward AH and Norton TT (2017a) Long-wavelength (red) light produces hyperopia in juvenile and adolescent tree shrews. *Vision Res* 140:55-65

Gee SS and Tabbara KF (1988) Increase in ocular axial length in patients with corneal opacification. *Ophthalmology* 95:1276-1278

Gifford KL, Richdale K, Kang P, Aller TA, Lam CS, Liu YM, *et al* (2019) IMI - Clinical Management Guidelines Report. *Invest Ophthalmol Vis Sci* 60(3):M184-M203

Gilmartin B, Nagra M and Logan NS (2013) Shape of the posterior vitreous chamber in human emmetropia and myopia. *Invest Ophthalmol Vis Sci* 54:7240-7251

Gisbert S and Schaeffel F (2018) M to L cone ratios determine eye sizes and baseline refractions in chickens. *Exp Eye Res* 172:104-111

Glasser A, Murphy CJ, Troilo D and Howland HC (1995) The mechanism of lenticular accommodation in chicks. *Vision Res* 35:1525-1540

Glasser A, Troilo D and Howland HC (1994) The mechanism of corneal accommodation in chicks. *Vision Res* 34:1549-1566

Gogate P and Wood M (2008) Recognising 'high-risk' eyes before cataract surgery. Community Eye Health Journal 21(65)12-14

Gordon RA and Donzis PB (1985) Refractive development of the human eye. *Arch Ophthalmol* 103:785-789

Goss DA and Winkler RL (1983) Progression of myopia in youth: age of cessation. *Am J Optom Physiol Opt* 60: 651–658

Goss DA (1991) Clinical accommodation and heterophoria findings preceding juvenile onset of myopia. *Optom Vis Sci* 68:110-116

Gottlieb MD, Fugate-Wentzek LA and Wallman J (1987) Different visual deprivations produce different ametropias and different eye shapes. *Invest Ophthalmol Vis Sci* 28:1225-1235

Goyal R, North RV and Morgan JE (2003) Comparison of laser interferometry and ultrasound A-scan in the measurement of axial length. *Acta Ophthalmol Scand* 81(4):331-335

Graham B and Judge SJ (1999) The effects of spectacle wear in infancy on eye growth and refractive error in the marmoset (Callithrix jacchus). *Vision Res* 39:189-206

Guyton DL, Greene PR, Scholz RT (1998) Dark-rearing interference with emmetropization in the rhesus monkey. *Invest Ophthalmol Vis Sci* 30:761-764

Gwiazda J, Bauer J, Thorn F and Held R (1995) Shifts in tonic accommodation after near work are related to refractive errors in children. *Ophthalmic Physiol Opt* 15:93-97

Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, *et al* (2003) A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children. *Invest Ophthalmol Vis Sci* 44: 1492–1500

Gwiazda JE, Hyman L, Norton TT, Hussein MEM, Marsh-Tootle W, Manny R *et al* (2004) Accommodation and Related Risk Factors Associated with Myopia Progression and Their Interaction with Treatment in COMET Children. *IOVS* 45:2143-2151

Gwiazda J, Thorn F, Bauer J et al (1993) Myopic children show insufficient accommodative response to blur. *Invest Ophthalmol Vis Sci* 34:690-694

Gwiazda J, Thorn F and Held R (2005) Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. *Optom Vis Sci* 82:273-278

Hasebe S, Jun J and Varnas SR (2014) Myopia control with positively aspherized progressive addition lenses: a 2-year, multicenter, randomized, controlled trial. *Invest Ophthalmol Vis Sci* 55:7177-7188

Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H and Khabazkhoob M (2018) Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. *J Curr Ophthalmol* 30(1):3-22

He JC, Sun P, Held R, Thorn F, Sun X and Gwiazda JE (2002) Wavefront aberrations in eyes of emmetropic and moderately myopic school children and young adults. *Vision Res* 42:1063-1070

Hiraoka T, Kakita T, Okamoto F, Takahashi H and Oshika T (2012) Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. *Invest Ophthalmol Vis Sci* 53:3913-3919

Hiraoka T, Kotsuka J, Kakita T, Okamoto F and Oshika T (2017) Relationship between higher-order wavefront aberrations and natural progression of myopia in schoolchildren. *Sci Rep* 7:7876

Hodos W and Kuenzel WJ (1984) Retinal-image degradation produces ocular enlargement in chicks. *Invest Ophthalmol Vis Sci* 25:652-659

Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo K, Sankaridurg P, *et al* (2016) Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology* 123:1036-1042

Holmes JM, Kraker RT, Beck RW, Birch EE, Cotter SA, Everett DF, *et al* (2003) A randomized trial of pre- scribed patching regimens for treatment of severe amblyopia in children. Ophthalmology 110:2075-2087

Howlett MH and McFadden SA (2006) Form-deprivation myopia in the guinea pig (Cavia porcellus). *Vision Res* 46:267-283

Huang J, Hung LF, Ramamirtham R, Blasdel T, Humbird TL, Bockhurst KH, *et al* (2009) Effects of form deprivation on peripheral refractions and ocular shape in infant rhesus monkeys (Macaca mulatta). *Invest Ophthalmol Vis Sci* 50:4033-4044

Hung LF, Arumugam B, She Z, Ostrin L and Smith III EL (2018) Narrow-band, long-wavelength lighting promotes hyperopia and retards vision-induced myopia in infant rhesus monkeys. *Exp Eye Res* 176:147-160

Hung LF, Crawford ML and Smith EL (1995) Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med* 1:761-765

Hussin HM, Spry PG, Majid MA and Gouws P (2006) Reliability and validity of the partial coherence interferometry for measurement of ocular axial length in children. *Eye (Lond)* 20(9):1021-1024

Huynh SC, Wang XY, Ip J, Robaei D, Kifley A, Rose KA, *et al* (2006) Prevalence and associations of anisometropia and aniso-astigmatism in a population based sample of 6 year old children. *Br J Ophthalmol* 90:597-601

Inagaki Y (1986) The rapid change of corneal curvature in the neonatal period and infancy. *Arch Ophthalmol* 104:1026-1027

Ingram RM (1977) Refraction as a basis for screening children for squint and amblyopia. *Br J Ophthalmol* 61:8-15

Ingram RM, Gill LE and Lambert TW (2000) Effect of spectacles on changes of spherical hypermetropia in infants who did, and did not, have strabismus. *Br J Ophthalmol* 84:324-326

Ip JM, Robaei D, Kifley A, Wang JJ, Rose KA and Mitchell P (2008) Prevalence of Hyperopia and Associations with Eye Findings in 6- and 12-Year-Olds. *Ophthalmology* 115:678-685

Irving EL, Callender MG and Sivak JG (1995) Inducing ametropias in hatchling chicks by defocus–aperture effects and cylindrical lenses. *Vision Res* 35:1165-1174

Irving EL, Sivak JG and CallenderMG (1992) Refractive plasticity of the developing chick eye. *Ophthalmic Physiol Opt* 12:448-456

Jiang L, Zhang S, Schaeffel F, Xiong S, Zheng Y, Zhou X, *et al* (2014) Interactions of chromatic and lens-induced defocus during visual control of eye growth in guinea pigs (Cavia porcellus). *Vision Res* 94:24-32

Jonas JB, Ang M, Cho P, Guggenheim JA, He MG, Jong M, *et al* (2021) IMI prevention of myopia and its progression. *Invest Ophthalmol Vis Sci* 62(5):6

Jones SM (2016) Interventions to limit the progression of myopia. PhD thesis, Aston University

Jones-Jordan L, Wang X, Scherer RW and Mutti DO (2020). Spectacle correction versus no spectacles for prevention of strabismus in hyperopic children. *Cochrane Database Syst Rev* Apr 2;4(4)

Jones LA, Mitchell GL, Mutti DO, Hayes JR, Moeschberger ML and Zadnik K (2005) Comparison of Ocular Component Growth Curves among Refractive Error Groups in Children. *Invest Ophthalmol Vis Sci* 46:2317-2327

Kageyama M, Hirooka K, Baba T and Shiraga F (2011) Comparison of ICare rebound tonometer with noncontact tonometer in healthy children. *J Glaucoma* 20(1):63-66

Kakita T, Hiraoka T and Oshika T (2011) Influence of overnight orthokeratology on axial elongation in childhood myopia. *Invest Ophthalmol Vis Sci* 52:2170-2174

Kang P, McAlinden C and Wildsoet CF (2017) Effects of multifocal soft contact lenses used to slow myopia progression on quality of vision in young adults. *Acta Ophthalmol* 95:e43-e45

Kang P and Swarbrick H (2011) Peripheral refraction in myopic children wearing orthokeratology and gas-permeable lenses. *Optom Vis Sci* 88:476-482

Kang P and Wildsoet C (2016) Acute and short-term changes in visual function with multifocal and soft contact lens wear in young adults. *Cont Lens Anterior Eye* 39(2):133-140

Katz J, Schein OD, Levy B, Cruiscullo T, Saw SM, Rajan U, *et al* (2003) A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. *Am J Ophthalmol* 136:82–90

Kawabata H, Murayama K and Adachi-Usami E (1996) Sensitivity loss in short wavelength sensitive cones in myopic eyes. *Nippon Ganka Gakkai Zasshi* 100:868-876

Kee CS, Hung LF, Qiao-Grider Y, Ramamirtham R, Winawer J, Wallman J, *et al* (2007) Temporal constraints on experimental emmetropization in infant monkeys. *Invest Ophthalmol Vis Sci* 48:957-962

Khambiphant B, Chatbunchachai N and Pongpirul K (2015) The effect of pupillary dilatation on IOL power measurement by using the IOLMaster. *Int Ophthalmol* 35:853-859

Khoo CY, Chong J and Rajan U (1999) A 3-year study on the effect of RGP contact lenses on myopic children. *Singap Med J* 40:230–237

Kielhorn I, Rajan MS, Tesha PM, Subryan VR, and Bell JA (2003) Clinical assessment of the Zeiss IOLMaster. *J Cataract Refract Surg* 29:518-522

Kim E, Bakaraju RC and Ehrmann K (2017) Power Profiles of Commercial Multifocal Soft Contact Lenses. *Optom Vis Sci* 94:183-196

Kimura S, Hasebe S, Miyata M, Hamasaki I and Ohtsuki H (2007) Axial length measurement using partial coherence interferometry in myopic children: Repeatability of the measurement and comparison with refractive components. *Jpn J Ophthalmol* 51:105-110

Kiorpes L and Wallman J (1995) Does Experimentally-induced Amblyopia Cause Hyperopia in Monkeys? *Vision Res* 35:1289–1297

Kir E, Tülin Berk A, Osman Saatci A, Kaynak S and Ergin MH (1998) Axial length and hyperopia in eyes with retinal vein occlusions. *Int Ophthalmol* 21:209-11

Kisilak ML, Campbell MC, Hunter JJ, Irving EL and Huang L (2006) Aberrations of chick eyes during normal growth and lens induction of myopia. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 192:845-855

Kleinstein RN, Jones LA, Hulett S, Kwon S, Lee RJ, Friedman NE, *et al* (2003) Refractive Error and Ethnicity in Children. *Arch Ophthalmol* 121(8):1141-1147

Klimek DL, Cruz OA, Scott WE and Davitt BV (2004) Isoametropic Amblyopia Due to High Hyperopia in Children. *J AAPOS* 8(4):310-313

Koch DD (1989) Glare and contrast sensitivity testing in cataract patients. *J Cataract Refract Surg* 15(2):158-164

Kröger RH and Wagner HJ (1996) The eye of the blue acara (Aequidens pulcher, Cichlidae) grows to compensate for defocus due to chromatic aberration. *J Comp Physiol A* 179:837-842

Kruger PB, Mathews S, Aggarwala KR and Sanchez N (1993) Chromatic aberration and ocular focus: Fincham revisited. *Vision Res* 33:1397-1411

Kulp MT, Ciner E, Maguire M, Pistilli M, Candy TR, Ying GS, Quinn G, *et al*; Vision in Preschoolers-Hyperopia in Preschoolers Study Group (2017) Attention and Visual Motor Integration in Young Children with Uncorrected Hyperopia. *Optom Vis Sci* 2017 94(10):965-970

Kulp MT, Ying GS, Huang J, Maguire M, Quinn G, Ciner EB, *et al* (2014) VIP Study Group. Associations between hyperopia and other vision and refractive error characteristics. *Optom Vis Sci* 91:383-389

Kunert KS, Peter M, Blum M, Haigis W, Sekundo W, Schütze J, *et al* (2016) Repeatability and agreement in optical biometry of a new swept-source optical coherence tomography–based biometer versus partial coherence interferometry and optical low-coherence reflectometry. *J Cataract Refract Surg* 42:76-83

Kyei S, Nketsiah AA, Asiedu K, Awuah A and Owusa-Ansah A (2017) Onset and duration of cycloplegic action of 1% cyclopentolate - 1% tropicamide combination. *Afri Health Sci* 17(3):923-932

Laojaroenwanit S, Layanun V, Praneeprachachon P and Pukrushpan P (2016) Time of maximum cycloplegia after instillation of cyclopentolate 1% in children with brown irises. *Clin Ophthalmol* 10:897-902

Lam AK, Chan R and Pang PC (2001) The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster. *Ophthalmic Physiol Opt* 21(6):477-483

Lam CSY, Tang WC, Tse DY-Y, Tang YY and To CH (2014) Defocus incorporated soft contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. *Br J Ophthalmol* 98:40-5

Lam CSY, Tang WC, Tse DY, Lee RPK, Chun RKM, Hasegawa K, *et al* (2019) Defocus Incorporated Multiple Segments (DIMS) spec- tacle lenses slow myopia progression: a 2-year randomised clinical trial. *Br J Ophthalmol* 104:363-368

Lam CSY, Tang WC, Lee PH, Zhang HY, Qi H, Hasegawa K, *et al* (2021) Myopia control effect of defocus incorporated multiple segments (DIMS) spectacle lens in Chinese children: results of a 3-year follow-up study. *Br J Ophthalmol* bjophthalmol-2020-317664

Larsen JS (1971a) The sagittal growth of the eye. 1. Ultrasonic measurement of the depth of the anterior chamber from birth to puberty. *Acta Ophthalmol (Copenh)* 49(2):239-262

Larsen JS (1971b) The sagittal growth of the eye. II. Ultrasonic measurement of the axial diameter of the lens and the anterior segment from birth to puberty. *Acta Ophthalmol (Copenh)* 49(3):427-440

Larsen JS (1971c) The sagittal growth of the eye. IV. Ultrasonic measurement of the axial length of the eye from birth to puberty. *Acta Ophthalmol (Copenh)* 49(6):873-886

Larsen JS (1971d) The sagittal growth of the eye. III. The sagittal growth of the eye. 3. Ultrasonic measurement of the posterior segment (axial length of the vitreous) from birth to puberty. *Acta Ophthalmol (Copenh)* 49(3):441-453

Lau JK, Vincent SJ, Collins MJ, Cheung SW and Cho P (2018) Ocular higher-order aberrations and axial eye growth in young Hong Kong children. *Sci Rep* 8(1):6726

Leat SJ (2011) To prescribe or not to prescribe? Guidelines for spectacle prescribing in infants and children. *Clin Exp Optom* 94(6):514-527

Lee TT and Cho P (2013) Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. *Ophthalmic Physiol Opt* 33:283293

Lepard CW (1975) Comparative changes in the error of refraction between fixing and amblyopic eyes during growth and development. *Am J Ophthalmol* 80:485-490

Leung JT and Brown B (1999) Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. *Optom Vis Sci* 76:346-354

Li Y, Wang J, Zhong X, Tian Z, Wu P, Zhao W, *et al* (2014) Refractive error and risk of early or late age-related macular degeneration: a systematic review and meta-analysis. *PloS one 9*(3):e90897

Li SM, Kang MT, Wu SS, Meng B, Sun YY, Wei SF, *et al* (2017) Studies using concentric ring bifocal and peripheral add multifocal contact lenses to slow myopia progression in school-aged children: a meta-analysis.
Ophthalmic Physiol Opt 37(1):51-9

Lim LS, Lamoureux E, Saw SM, Tay WT, Mitchell P and Wong TY (2010) Are myopic eyes less likely to have diabetic retinopathy? *Ophthalmology* 117:524-530

Lim R, Mitchel P and Cumming RG (1999) Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* 40:3021-3026

Limpert E, Stahel WA, Abbt M (2001) Log-normal distributions across the sciences: keys and clues. *Bioscience* 51:341–352

Lin LLK, Shih YF, Hsiao CK and Chen CJ (2004) Prevalence of Myopia in Taiwanese Schoolchildren: 1983 to 2000. *Ann Acad Med Singapore* 33:27-33

Lipson MJ, Brooks MM and Koffler BH (2018) The role of orthokeratology in myopia control: a review. *Eye Contact Lens* 44:224-230

Liu Y and Wildsoet C (2011) The effect of two-zone concentric bifocal spectacle lenses on refractive error development and eye growth in young chicks. *Invest Ophthalmol Vis Sci* 52:1078-1086

Liu Y and Wildsoet C (2012) The effective add inherent in 2-zone negative lenses inhibits eye growth in myopic young chicks. *Invest Ophthalmol Vis Sci* 53: 5085-5093

Liu R, Qian YF, He JC, Hu M, Zhou XT, Dai JH, *et al* (2011) Effects of different monochromatic lights on refractive development and eye growth in Guinea pigs. *Exp Eye Res* 92:447-453
Lixia L, Weizhong L, Yunru L, Feng Z, Chen C and Zhikuan Y (2013) Treatment Outcomes of Myopic Anisometropia with 1% Atropine: A Pilot Study. *Optom Vis Sci* 90:1486-1492

Llorente L, Barbero S, Cano D, Dorronsoro C and Marcos S (2004) Myopic versus hyperopic eyes: axial length, corneal shape and optical aberrations. *J Vis* 4:288-298

Logan NS, Davies LN, Mallen EA and Gilmartin B (2005) Ametropia and ocular biometry in a U.K. university student population. *Optom Vis Sci* 82:261-266

Logan NS, Radhakrishnan H, Cruickshank FE, Allen PM, Bandela PK, Davies LN, *et al* (2021) IMI Accommodation and binocular vision in myopia development and progression. *Invest Ophthalmol Vis Sci* 62(5):4

Logan NS and Wolffsohn JS (2020) Role of un-correction, under-correction and over-correction of myopia as a strategy for slowing myopic progression. *Clin Exp Optom* 103:133-137

Logan NS, Shah P, Rudnicka AR, Gilmartin B and Owen CG (2011) Childhood ethnic differences in ametropia and ocular biometry: the Aston Eye Study. *Ophthalmic Physiol Opt* 31:550-558

Lopes-Ferreira D, Neves H, Queiros A, Faria-Ribeiro M, Peixoto-de-Matos SC and González-Méijome JM (2013) Ocular Dominance and Visual Function Testing. *Biomed Res Int* 238943

Lopez-Gil N, Iglesias I and Artal P (1998) Retinal image quality in the human eye as a function of the accommodation. *Vision Res* 38:2897-2907

Lowe RF (1970) Aetiology of the anatomical basis for primary angle-closure glaucoma. Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. *Br J Ophthalmol* 54:161-169

Maldonado-Codina C, Morgan PB, Schnider CM and Efron N (2004) Short-Term Physiologic Response in Neophyte Subjects Fitted with Hydrogel and Silicone Hydrogel Contact Lenses. *Optom Vis Sci* 81:911-921

Mallen EAH, Gilmartin B, Wolffsohn JS and Tsujimura S (2015) Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults: an update. *Ophthalmic Physiol Opt* 35:622-627

Mallen EAH, Wolffsohn JS, Gilmartin B and Tsujimura S (2001) Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic Physiol Opt* 21(2):101-107

Manny RE, Fern KD, Zervas HJ, Cline GE, Scott SK, White JM, *et al* (1993) 1% Cyclopentolate Hydrochloride: Another Look at the Time Course of Cycloplegia Using An Objective Measure of the Accommodative Response. *Optom Vis Sci* 70(8):651-665

Matsumara H and Hirai H (1999) Prevalence of Myopia and Refractive Changes in Students From 3 to 17 Years of Age. *Surv Ophthalmol* 44(1)S109-S115

Mayer DL, Hansen RM, Moore BD, Kim S and Fulton AB (2001) Cycloplegic refractions in healthy children aged 1 through 48 months. *Arch Ophthalmol* 119:1625-1628

McBrien NA and Millodot M (1987) The relationship between tonic accommodation and refractive error. *Invest Ophthalmol Vis Sci* 28:997-1004

McBrien NA, Moghaddam HO and Reeder AP (1993) Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci* 34:205-215

McCullough SJ, Adamson G, Breslin KMM, McClelland JF, Doyle LD and Saunders KJ (2020) Axial growth and refractive change in white European children and young adults: predictive factors for myopia. *Nature* 10:15189

McCullough SJ, O'Donoghue L and Saunders KJ (2016) Six Year Refractive Change among White Children and Young Adults: Evidence for Significant Increase in Myopia among White UK Children. PLos One 11(1):e0146332

McFadden SA, Tse DY, Bowrey HE, Leotta AJ, Lam CS, Wildsoet CF, *et al* (2014) Integration of defocus by dual power Fresnel lenses inhibits myopia in the mammalian eye. *Invest Ophthalmol Vis Sci* 55:908-917

McGraw P, Winn B, Whitaker D (1995) Reliability of the Snellen chart. *BMJ* 310:1481-1482

Millodot M (1981) Effect of ametropia on peripheral refraction. *Am J Optom Physiol Opt* 58:691-695

Moderiano D, Do M, Hobbs S, Lam VY, Sarin S, Alonso-Caneiro D, *et al* (2019) Influence of the time of day on axial length and choroidal thickness changes to hyperopic and myopic defocus in human eyes. *Exp Eye Res* 182:125-136

Mohan K and Sharma A (2011) Optimal dosage of cyclopentolate 1% for cycloplegic refraction in hypermetropes with brown irides. Indian J Ophthalmol 59(6):514-516

Momeni-Moghaddam H, Maddah N, Wolffsohn J, Etezad-Razavi M, Zarei-Ghanavati S, Rezayat AA, *et al* (2019) The Effect of Cycloplegia on the Ocular Biometric and Anterior Segment Parameters: A Cross-Sectional Study. *Ophthalmol Ther* 8:387-395

Moore KE and Berntsen DA (2014) Central and Peripheral Autorefraction Repeatability in Normal Eyes. *Optom Vis Sci* 4(91):1106-1112

Morgan IG and Ambadeniya MP (2006) Imposed peripheral myopic defocus can prevent the development of lens–induced myopia. *Invest Ophthalmol Vis Sci* 47:3328

Morgan IG, Ashby RS and Nickla DL (2013) Form deprivation and lens-induced myopia: are they different? *Ophthalmic Physiol Opt* 33:355-361

Morgan IG, Wu P-C, Ostrin LA, Tideman WL, Yam JC, Lan W *et al* (2021) IMI Risk factors for myopia. Invest Ophthalmol Vis Sci 62(5):3

Mutti DO (2007) To emmetropize or not to emmetropize? The question for hyperopic development. *Optom Vis Sci* 84:97-102

Mutti DO, Mitchell GL, Hayes JR et al. (2006) Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci* 47:837-846

Mutti DO, Mitchell GL, Jones LA, Friedman NE, Frane SL, Lin WK, *et al* (2005) Axial Growth and Changes in Lenticular and Corneal Power during Emmetropization in Infants. *Invest Ophthalmol Vis Sci* 46(9):3074-3080

Mutti DO, Mitchell GL, Jones LA, Friedman NE, Frane SL, Lin WK, *et al* (2009) Accommodation, Acuity, and their Relationship to Emmetropization in Infants. *Optom Vis Sci* 86(6):666-676

Mutti DO, Mitchell GL, Sinnott LT, Jones-Jordan LA, Moeschberger ML, Cotter SA, *et al* (2012) Corneal and Crystalline Lens Dimensions Before and After Myopia Onset. *Optom Vis Sci* 89:251-262

Mutti DO, Sholtz RI, Friedman NE and Zadnik K (2000) Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci* 41:1022-1030

Mutti DO, Sinnott LT, Mitchell GL, Jones-Jordan LA, Moeschberger ML, Cotter SA, et al (2011) Relative peripheral refractive error and the risk of onset and progression of myopia in children. *Invest Ophthalmol Vis Sci* 52:199-205

Mutti DO, Sinnott LT, Reuter KS, Walker MK, Berntsen DA, Jones-Jordan LA, *et al* (2019) Peripheral refraction and eye lengths in myopic children in the bifocal lenses in nearsighted kids (BLINK) study. *Transl Vis Sci Technol* 8:17

Mutti DO, Zadnik K, Egashira S, Kish L (1994) The Effect of Cycloplegia on Measurement of the Ocular Components. *Invest Ophthalmol Vis Sci* 35(2):515-527

Nabie R, Andalib D, Khojasteh H and Aslanzadeh SA (2019) Comparison of the Effect of Different Types of Experimental Anisometropia on Stereopsis Measured with Titmus, Randot and TNO Stereotests. *J Ophthalmic Vis Res* 14(1):48-51

Narayanasamy S, Vincent SJ, Sampson GP, Wood JM (2014) Simulated hyperopic anisometropia and reading, visual information processing, and reading-related eye movement performance in children. *Invest Ophthalmol Vis Sci* 55:8015-8023

Nastri G, Perugini GC, Savastano S, Polzella A and Sbordone G (1984) The evolution of refraction in the fixing and the amblyopic eye. *Doc Ophthalmol* 56:265–274

Negrel AD, Maul E, Pokharel GP, Zhao J, Ellwein LB (2000) Refractive Error Study in Children: sampling and measurement methods for a multi-country survey. *Am J Ophthalmol* 129(4):421-6

Németh J, Fekete O and Pesztenlehrer N (2003) Optical and ultrasound measurement of axial length and anterior chamber depth for intraocular lens power calculation. *J Cataract Refract Surg* 29(1)85-88

Németh J, Tapasztó B, Aclimandos WA, Kestelyn P, Jonas JB, De Faber JHN, *et al* (2021) Update and guidance on management of myopia. European Society of Ophthalmology in cooperation with International Myopia Institute. *Eur J Ophthalmol* 31(3):853-883

Nickla DL, Thai P, Zanzerkia Trahan R and Totonelly K (2017) Myopic defocus in the evening is more effective at inhibiting eye growth than defocus in the morning: effects on rhythms in axial length and choroid thickness in chicks. *Exp Eye Res* 154:104-115

Norton TT, Siegwart JT Jr. and Amedo AO (2006) Effectiveness of Hyperopic Defocus, Minimal defocus, or Myopic Defocus in Competition with a Myopiagenic Stimulus in Tree Shrew Eyes. *Invest Ophthalmol Vis Sci* 47:4687–4699

O'Donoghue LO, Kapetanankis VV, McClelland JF, Logan NS, Owen CG, Saunders KJ, *et al* (2015) Risk Factors for Childhood Myopia: Findings From the NICER Study. *Invest Ophthalmol Vis* 56:1524-1530

O'Donoghue LO, McClelland JF, Logan NS, Rudnicka AR, Owen CG and Saunders KJ (2013) Profile of Anisometropia and Aniso-Astigmatism in Children: Prevalence and Association with Age, Ocular Biometric Measures, and Refractive Status. *Invest Ophthalmol Vis Sci* 54:602-608

O'Donoghue L, Rudnicka AR, McClelland JF, Logan NS and Saunders KJ (2012) Visual Acuity Measures Do Not Reliably Detect Childhood Refractive Error - an Epidemiological Study. *PLoS ONE* 7(3): e34441

Ohno-Matsui K, Wu P-C, Yamashiro K, Vutipongsatorn K, Fang Y, Cheung CMG *et al* (2021) IMI Pathologic Myopia. *Invest Ophthalmol Vis Sci* 62(5):5

O'Leary DJ and Millodot M (1979) Eyelid closure causes myopia in humans. Experientia 35:1478-1479

Ostrin LA and Glasser A (2010) Autonomic drugs and the accommodative system in rhesus monkeys. *Exp Eye Res* 90:104-112

Ostrin LA, Liu Y, Choh V and Wildsoet CF (2011) The role of the iris in chick accommodation. *Invest Ophthalmol Vis Sci* 52:4710-4716

Ostrin LA (2017) Objectively measured light exposure in emmetropic and myopic adults. *Optom Vis Sci* 94:229-238

Ostrin LA (2018) The ipRGC-driven pupil response with light exposure and refractive error in children. *Ophthalmic Physiol Opt* 38:503-515

Pai AS, Rose KA, Leone JF, Sharbini S, Burlutsky G, Varma R, *et al* (2012) Amblyopia prevalence and risk factors in Australian preschool children. *Ophthalmology* 119(1):138-144

Papastergiou GI, Schmid GF, Laties AM, Pendrak K, Lin T and Stone RA (1998) Induction of axial eye elongation and myopic refractive shift in one-year-old chickens. *Vision Res* 38:1883-1888

Paquin MP, Hamam H, Simonet P (2002) Objective measurement of optical aberrations in myopic eyes. *Optom Vis Sci* 79:285-291

Pauné J, Morales H, Armengol J, Quevedo L, Faria-Ribeiro M and González-Méijome JM (2015) Myopia control with a novel peripheral gradient soft lens and orthokeratology: a 2-year clinical trial. *Biomed Res Int* 2015:507572

Pediatric Eye Disease Investigator Group (2002) A randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 120:268-278

Pelli DG and Bex P (2013) Measuring contrast sensitivity. *Vision Res* 20:10-14

Perrigin J, Perrigin D, Quintero S and Grosvenor T (1990) Silicone-acrylate contact lenses for myopia control: 3-year results. *Optom Vis Sci* 67:764-769

Plainis S, Atchison DA and Charman NW (2013) Power Profiles of Multifocal Contact Lenses and Their Interpretation. *Optom Vis Sci* 90:1066-1077

Portal JM and Romano PE (1998) Major review: ocular sighting dominance: a review and a study of athletic proficiency and eye-hand dominance in a collegiate baseball team. *Binocul Vis Strabismus Q* 13(2):125-132

Przekoracka K, Michalak K, Olszewski J, Zeri F, Michalski A, Paluch J, et al (2020) Contrast sensitivity and visual acuity in subjects wearing multifocal contact lenses with high additions designed for myopia progression control. *Cont Lens Anterior Eye* 43(1):33-39

Ruiz-Pomeda A, Pérez-Sánchez B, Valls I, Prieto-Garrido FL, Gutiérrez-Ortega R and Villa-Collar C (2018) MiSight Assessment Study Spain (MASS). A 2-year randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 256:1011-1021

Rutstein RP and Corliss D (1999) Relationship between anisometropia, amblyopia, and binocularity. *Optom Vis Sci* 76(4):229-233

Qiao-Grider Y, Hung LF, Kee CS, Ramamirtham R and Smith III EL (2004) Recovery from form-deprivation myopia in rhesus monkeys. *Invest Ophthalmol Vis Sci* 45:3361-3372

Qin XJ, Margrain TH, To CH, Bromham N, Guggenheim JA (2005) Anisometropia is independently associated with both spherical and cylindrical ametropia. *Invest Ophthalmol Vis Sci* 46: 4024–4031

Raasch TW, Bailey IL and Bullimore MA (1998) Repeatability of Visual Acuity Measurement. *Optom Vis Sci* 75(5):342-348

Ramamirtham R, Kee CS, Hung LF, Qiao-Grider Y, Roorda A and Smith III EL (2006) Monochromatic ocular wave aberrations in young monkeys. *Vision Res* 46:3616-3633

Ramamirtham R, Kee CS, Hung LF, Qiao-Grider Y, Huang J, Roorda A, *et al* (2007) Wave aberrations in rhesus monkeys with vision-induced ametropias. *Vision Res* 47:2751-2766

Raviola E and Wiesel TN (1990) Neural control of eye growth and experimental myopia in primates. Ciba Found Symp 155:22-38

Repka MX, Beck RW, Holmes JM, Birch EE, Chandler DL, Cotter SA, *et al* (2003) A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol* 121:603-11

Robaei D, Rose KA, Ojaimi E, Kifley A, Martin FJ and Mitchell P (2006) Causes and associations of amblyopia in a population-based sample of 6-year-old Australian children. *Arch Ophthalmol* 124(6):878-884

Roberts CJ and Adams GGW (2002) Contact lenses in the management of high anisometropic amblyopia. *Eye* 16:577-579

Romano PE and von Noorden GK (1999) Knapp's law and unilateral axial high myopia. 1970. *Binocul Vis Strabismus* 14(3):215-222

Roorda A and Williams DR (1999) The arrangement of the three cone classes in the living human eye. *Nature* 397:520-522

Rose LT and Moshegov CN (2003) Comparison of the Zeiss IOLMaster and applanation A-scan ultrasound: biometry for intraocular lens calculation. *Clin Experiment Ophthalmol* 31(2): 121-124

Rosenfield M and Cohen AS (1996) Repeatability of clinical measurements of the amplitude of accommodation. *Ophthalmic Physiol Opt* 16(3):247-249a

Rotolo M, Montani G and Martin R (2017) Myopia onset and role of peripheral refraction. *Clin Optom (Auckl)* 9:105-111

Royal College of Ophthalmologists (2006) Guidelines for the Management of Amblyopia

Rucker FJ and Osorio D (2008) The effects of longitudinal chromatic aberration and a shift in the peak of the middle-wavelength sensitive cone fundamental on cone contrast. *Vision Res* 48:1929-1939

Rucker FJ (2013) The role of luminance and chromatic cues in emmetropisation. *Ophthalmic Physiol Opt* 33:196-214

Rucker FJ and Wallman J (2009) Chick eyes compensate for chromatic simulations of hyperopic and myopic defocus: evidence that the eye uses longitudinal chromatic aberration to guide eye-growth. *Vision Res* 49:1775-1783

Ruiz-Pomeda A, Pérez-Sánchez B, Cañadas P, Prieto-Garrido FL, Gutiérrez-Ortega R and Villa-Collar C (2019) Binocular and accommodative function in the controlled randomized clinical trial MiSight® Assessment Study Spain (MASS). *Graefes Arch Clin Exp Ophthalmol* 257(1):207-215

Sankaridurg P, Donovan L, Varnas S, Ho A, Chen X, Martinez A, *et al* (2010) Spectacle Lenses Designed to Reduce Progression of Myopia: 12-Month Results. *Optom Vis Sci* 87(9):631-641

Sankaridurg P, He X, Naduvilath T, Lv M, Ho A, Smith III E, *et al* (2017) Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. *Acta Ophthalmol* 95:e633-e640

Sankaridurg P, Holden B, Smith III E, Nadwilath T, Chen X, Lazon de la Jara P, *et al* (2011) Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. *Invest Ophthalmol Vis Sci* 52:9362-9367

Sankaridurg P, Tahhan N, Kandel H, Naduvilah T, Zou H, Frick KD, *et al* (2021) IMI Impact of myopia. Invest Ophthalmol Vis Sci 62(5):2

Santodomingo-Rubido J, Mallen EA, Gilmartin B and Wolffsohn JS (2002) A new non-contact optical device for ocular biometry. *Br J Ophthalmol* 86:458-462

Santodomingo-Rubido J, Villa-Collar C, Gilmartin B and Gutiérrez-Ortega R (2012) Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. *Invest Ophthalmol Vis Sci* 53:5060-5065

Saunders KJ, Woodhouse JM and Westall CA (1995) Emmetropisation in Human Infancy: Rate of Change is Related to Initial Refractive Error. *Vision Res* 35:1325–1328

Schaeffel F, Glasser A and Howland HC (1988) Accommodation, refractive error and eye growth in chickens. *Vision Res* 28:639-657

Schaeffel F, Troilo D, Wallman J and Howland HC (1990) Developing eyes that lack accommodation grow to compensate for imposed defocus. *Vis Neurosci* 4:177-183

Schippert R and Schaeffel F (2006) Peripheral defocus does not necessarily affect central refractive development. *Vision Res* 46:3935-3940

Schmid GF (2011) Association between retinal steepness and central myopic shift in children. *Optom Vis Sci* 88:684-690

Schmid KL and Wildsoet CF (1996) Effects on the compensatory responses to positive and negative lenses of intermittent lens wear and ciliary nerve section in chicks. *Vision Res* 36:1023-1036
Seidemann A and Schaeffel F (2002) Effects of longitudinal chromatic aberration on accommodation and emmetropization. *Vision Res* 42:2409-2417

Seidemann A, Schaeffel F, Guirao A, Lopez-Gil N and Artal P (2002) Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A Opt Image Sci Vis* 19:2363-2373

Senthil S, Garudadri C, Khanna RC and Sannapaneni K (2010) Angle closure in the Andhra Pradesh Eye Disease Study. *Ophthalmology* 117:1729-1735

Sha J, Bakaraju RC, Tilia D, Chung J, Delaney S, Munro A, *et al* (2016) *Arq Bras Oftalmol* 79(2):73-77

Shaikh AW, Siegwart JT Jr and Norton TT (1999) Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optom Vis Sci* 76:308-315

Shaw DE, Fielder AR, Minshull C and Rosenthal AR (1988) Amblyopia--factors influencing age of presentation. *Lancet* 2(8604):207-209

Shen W, Vijayan M and Sivak J (2005) Inducing form-deprivation myopia in fish. *Invest Ophthalmol Vis Sci* 46:1797-1803

Sheng H, Bottjer CA, Bullimore MA (2004) Ocular component measurement using the Zeiss IOLMaster. *Optom Vis Sci* 81:27-34

Sheppard AL and Davies LN (2010) Clinical evaluation of the Grand Seiko Auto Ref/Keratometer WAM-5500. *Ophthalmic Physiol Opt* 30:143-151

Sherman SM, Norton TT and Casagrande VA (1977) Casagrande VA. Myopia in the lid-sutured tree shrew (Tupaia glis). *Brain Res* 124:154-157

Shih YF, Hsiao CK, Chen CJ, Change CW, Hung PT and Lin LLK (2001) An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand* 79:233-236

Shih YF, Hsiao CH, Wen SH, Lin LL, Chen CJ and Hung PT (2005) Prevalence of anisometropia in Taiwanese schoolchildren. *J Formos Med Assoc* 104:412-417

Siderov J and Tiu A (1999) Variability of measurements of visual acuity in a large eye clinic *Acta Ophthalmol Scand* 77(6):673-676

Siegwart JT Jr and Norton TT (1998) The susceptible period for deprivation-induced myopia in tree shrew. *Vision Res* 38:3505-3515

Smith III EL (1998) Spectacle lenses and emmetropization: the role of optical defocus in regulating ocular development. *Optom Vis Sci* 75:388-398

Smith III EL, Bradley DV, Fernandes A and Boothe RG (1999) Form deprivation myopia in adolescent monkeys. *Optom Vis Sci* 76:428-432

Smith III EL and Hung LF (1999) The role of optical defocus in regulating refractive development in infant monkeys. *Vision Res* 39:1415-1435

Smith III EL, Hung LF, Arumugam B, Holden B, Neitz M and Neitz J (2015) Effects of long-wavelength lighting on refractive development in infant rhesus monkeys. *Invest Ophthalmol Vis Sci* 56:6490-6500

Smith III EL, Hung LF and Harwerth RS (1994) Effects of optically induced blur on the refractive status of young monkeys. *Vision Res* 34:293-301

Smith III EL, Hung LF and Harwerth RS (1999) Developmental visual system anomalies and the limits of emmetropization. *Ophthalmic Physiol Opt* 1999; 19: 90–102

Smith III EL, Hung LF and Huang J (2009) Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res* 49:2386-2392

Smith III EL, Hung LF and Huang J (2012) Protective effects of high ambient lighting on the development of form- deprivation myopia in rhesus monkeys. *Invest Ophthalmol Vis Sci* 53:421-428

Smith III EL, Hung LF, Huang J and Arumugam B (2013) Effects of local myopic defocus on refractive development in monkeys. *Optom Vis Sci* 90:1176-1186

Smith III EL, Huang J, Hung LF, Blasdel TL, Humbird TL and Bockhurst KH (2009) Hemiretinal form deprivation: evidence for local control of eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci* 50:5057-5069

Smith III EL, Hung LF, Huang J, Blasdel TL, Humbird TL and Bockhurst KH (2010) Effects of optical defocus on refractive development in monkeys: evidence for local, regionally selective mechanisms. *Invest Ophthalmol Vis Sci* 51:3864-3873

Smith III EL, Hung LF, Kee CS, Kee C and Qiao Y (2002) Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Invest Ophthalmol Vis Sci* 43:291-299

Smith III EL, Kee CS, Ramamirtham R, Qiao-Grider Y and Hung LF (2005) Peripheral vision can influence eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci* 46:3965-3972

Smith III EL, Ramamirtham R, Qiao-Grider Y, Hung LF, Huang J, Kee CS, *et al* (2007) Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci* 48: 3914-3922

Sng CC, Lin XY, Gazzard G, Chang B, Dirani M, Chia A, *et al* (2011a) Peripheral refraction and refractive error in Singapore Chinese children. *Invest Ophthalmol Vis Sci* 52:1181-1190

Sng CC, Lin XY, Gazzard G et al (2011b) Change in peripheral refraction over time in Singapore Chinese children. *Invest Ophthalmol Vis Sci* 52:7880-7887

Sokol S, Moskowitz A and Paul A (1983) Evoked potential estimates of visual accommodation in infants. *Vision Res* 23:851-860

Sorsby A, Benjamin B, Sheridan M, Stone J and Leary GA (1961) Refraction and its components during the growth of the eye from the age of three. *Memo Med Res Counc* 301 (Special):1-67

Sorsby A and Leary GA (1969) A longitudinal study of refraction and its components during growth. *Spec Rep Ser Med Res Counc* (GB) 309:1-41
Sterner B, Gellerstedt M and Sjöström A (2004) The amplitude of accommodation in 6–10-year-old children – not as good as expected! *Ophthalmic Physiol Opt* 24:246-251

Stone J (1976) The possible influence of contact lenses on myopia. *Br J Physiol Opt* 31:89-114

Strang NC, Schmid KL, Carney LG (1998) Hyperopia is predominantly axial in nature. *Curr Eye Res* 17:380-3

Sun Y-Y, Li S-M, Li S-Y, Kang MT, Liu LR, Meng B, *et al* (2017) Effect of uncorrection versus full correction on myopia
progression in 12-year-old children. *Graefes Arch Clin Exp Ophthalmol* 255:189-95

Swarbrick HA (2006) Orthokeratology review and update. *Clin Exp Optom* 89:124-143

Szigeti A, Schneider M, Ecsedy M, Nagy ZZ and Récsán Z (2015) Association between retinal vein occlusion, axial length and vitreous chamber depth measured by optical low coherence reflectometry. *BMC Ophthalmol* 15(45):1-7

Tahhan N, Du Toit R, Papas E, Chung H, Hood DLA and Holden B (2003) Comparison of reverse-geometry lens designs for over-night orthokeratology. *Optom Vis Sci* 80:796-804

Tang WC, Leung M, Wong ACK, To CH and Lam CSY (2020) Optical Interventions For Myopia Control. Springer Open

Tanlamai T and Goss DA (1979) Prevalence of monocular amblyopia among anisometropes. *Am J Optom Physiol Opt* 56(11):704-715

Tarczy-Hornoch K, Varma R, Cotter SA, McKean-Cowdin R, Lin JH, Borchert MS, *et al* (2011) Risk factors for decreased visual acuity in preschool children: the multi-ethnic pediatric eye disease and Baltimore pediatric eye disease studies. *Ophthalmology* 118:2262-2273

The College of Optometrists. Guidance for Professional Practice. https://guidance.college-optometrists.org/home/ [Accessed 11/12/2020]

The Royal College of Ophthalmologists Guidelines for the management of strabismus in childhood, 2012. https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2012-SCI-250-Guidelines-for-Management-of-Strabismus-in-Childhood- 2012.pdf [Accessed 8 August 2020]

Thibos LN, Bradley A, Hong X (2002) A statistical model of the aberration structure of normal, well-corrected eyes. *Ophthalmic Physiol Opt* 22:427-433

Thorn F, Gwiazda J and Held R (2005) Myopia Progression is Specified by a Double Exponential Growth Function. *Optom Vis Sci* 82:286-297

Tidbury LP, Czanner G and Newsham (2016) Fiat Lux: the effect of illuminance on acuity testing. *Graefes Arch Clin Exp Ophthalmol* 254:1091-1097

Tkatchenko TV, Shen Y and Tkatchenko AV (2010) Mouse experimental myopia has features of primate myopia. *Invest Ophthalmol Vis Sci* 51:1297-1303

Tondel GM and Candy TR (2007) Human Infants' Accommodation Responses to Dynamic Stimuli. *Invest Ophthalmol Vis Sci* 48:949-956

Tong L, Chan YH, Gazzard G, Tan D and Saw SM (2006) Longitudinal study of anisometropia in Singaporean school children. *Invest Ophthalmol Vis Sci* 47:3247-3252

Torii H, Kurihara T, Seko Y, Negishi K, Ohnuma K, Inaba T, *et al* (2017) Violet light exposure can be a preventive strategy against myopia progression. *EBioMedicine* 15:210-219

Totonelly KC, Coletta NJ and Troilo D (2006) Lens-induced refractive errors alter the pattern of peripheral refractive state in marmosets. *Invest Ophthalmol Vis Sci* 47:3323

Totonelly K and Troilo D (2008) Eye shape and off-axis refractive state following induced axial refractive errors in marmoset monkeys. *Invest Ophthalmol Vis Sci* 49:3589

Troilo D, Nickla DL and Wildsoet CF (2000) Form deprivation myopia in mature common marmosets (Callithrix jacchus). *Invest Ophthalmol Vis Sci* 41:2043-2049
Troilo D, Quinn N and Baker K (2007) Accommodation and induced myopia in marmosets. *Vision Res* 47:1228-1244

Trolio D, Smith III EL, Nickla DL, Ashby R, Tkatchenko AV, Ostrin LA, *et al* (2019) IMI - Report on Experimental Models of Emmetropization and Myopia. *Invest Ophthalmol Vis Sci* 60:M31-M88

Troilo D, Totonelly K and Harb EN (2009) Imposed anisometropia, accommodation, and regulation of refractive state. *Optom Vis Sci* 86:31-39

Troilo D and Wallman J (1987) Changes in corneal curvature during accommodation in chicks. *Vision Res* 27:241-247

Troilo D and Wallman J (1991) The regulation of eye growth and refractive state: an experimental study of emmetropization. *Vision Res* 31:1237-1250

Tse DY, Lam CS, Guggenheim JA, Lam C, Li K, Liu Q, *et al* (2007) Simultaneous defocus integration during refractive development. *Invest Ophthalmol Vis Sci* 48:5352-5359

Van Doorn LLA, Evans BJW, Edgar DF, and Fortuin MF (2014) Manufacturer changes lead to clinically important differences between two editions of the TNO stereotest. *Ophthalmic Physiol Opt* 34(2):243-249

Vancleef K and Read JCA (2019) Which Stereotest do You Use? A Survey Research Study in the British Isles, the United States and Canada. *Brit Irish Orthop J* 15(1):15-24

Verkicharla PK, Mathur A, Mallen EAH, Pope JM and Atchison DA (2012) Eye shape and retinal shape, and their relation to peripheral refraction. *Ophthalmic Physiol Opt* 32:184-199

Verkicharla PK, Suheimat M, Schmid KL and Atchison DA (2016) Peripheral refraction, peripheral eye length and retinal shape in myopia. *Optom Vis Sci* 93:1072-1078

Verkicharla PK, Suheimat M, Schmid KL and Atchison DA (2017) Differences in retinal shape between East Asian and Caucasian eyes. *Ophthalmic Physiol Opt* 37:275-283

Vilupuru AS, Roorda A and Glasser A (2004) Spatially variant changes in lens power during ocular accommodation in a rhesus monkey eye. *J Vis* 4:299-309

von Noorden GK and Lewis RA (1987) Ocular axial length in unilateral congenital cataracts and blepharoptosis. *Invest Ophthalmol Vis Sci* 28:750-752
Walline JJ, Greiner KL, McVey ME and Jones-Jordan LA (2013) Multifocal contact lens myopia control. *Optom Vis Sci* 90:1207-1214

Wagner S, Conrad F, Bakaraju RC, Fedtke C, Ehrmann K, Holden BA (2015) Power profiles of single vision and multifocal soft contact lenses. *Cont Lens Anterior Eye* 38(1):2-14

Walline JJ, Jones LA and Sinnott LT (2009) Corneal reshaping and myopia progression. *Br J Ophthalmol* 93:1181-1185

Walline JJ, Jones LA, Mutti DO and Zadnik K (2004) A randomized trial of the effects of rigid contact lenses on myopia progression. *Arch Ophthalmol* 122:1760-1766

Walline JJ (2016) Myopia control: a review. *Eye Contact Lens* 42(1):3-8

Walline JJ, Walker MK, Mutti DO, Jones-Jordan LA, Sinnott LT, Giannoni AG, *et al* (2020) Effect of High Add Power, Medium Add Power, or Single-Vision Contact Lenses on Myopia Progression in Children: The BLINK Randomized Clinical Trial. *JAMA* 324(6):571–580

Wallman J and Adams JI (1987) Developmental aspects of experimental myopia in chicks: susceptibility, recovery and relation to emmetropization. *Vision Res* 27:1139-1163

Wallman J, Gottlieb MD, Rajaram V and Fugate-Wentzel LA (1987) Local retinal regions control local eye growth and myopia. *Science* 237:73-77

Wallman J, Ledoux C and Friedman MB (1978) Simple devices for restricting the visual fields of birds. *Behav Res Methods Instrum* 10:401-403

Wallman J, Turkel J and Trachtman J (1978) Extreme myopia produced by modest change in early visual experience. *Science* 201:1249-1251

Wallman J, Wildsoet C, Xu A, Gottlieb MD, Nickla DL, Marran L, *et al* (1995) Moving the retina: choroidal modulation of refractive state. *Vision Res* 35:37-50

Watanabe S, Yamashita T, Ohba N (1999) A longitudinal study of cycloplegic refraction in a cohort of 350 Japanese schoolchildren. Cycloplegic refraction. *Ophthalmic Physiol Opt* 19:22-29

Wiesel TN, Raviola E (1977) Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature* 266:66-68

Wiesel TN and Raviola E (1979) Increase in axial length of the macaque monkey eye after corneal opacification. *Invest Ophthalmol Vis Sci* 18:1232-1236

Wildsoet CF and Schmid KL (2000) Optical correction of form deprivation myopia inhibits refractive recovery in chick eyes with intact or sectioned optic nerves. *Vision Res* 40:3273-3282

Wildsoet C and Wallman J (1995) Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Res* 35:1175-1194

Williams WR, Latif AH, Hannington L, Watkins DR (2005) Hyperopia and educational attainment in a primary school cohort. *Arch Dis Child* 90:150–153

Wilson J and Sherman S (1977) Differential effects of early monocular deprivation on binocular and monocular segments of cat striate cortex. *J Neurophysiol* 40:891-903

Winawer J, Zhu X, Choi J and Wallman J (2005) Ocular compensation for alternating myopic and hyperopic defocus. *Vision Res* 45:1667-1677

Winn B, Ackerley RG, Brown CA, Murray FK, Prais J and John MF (1986) The superiority of contact lenses in the correction St of all anisometropia. *J BCLA* 9:95-100

Winn B, Ackerley RG, Brown CA, Murray FK, Prais J and John MF (1988) Reduced aniseikonia in axial anisometropia with contact lens correction. *Ophthal Physiol Opt* 8:341-344

Wolffsohn JS, Jong M, Smith EL, Resnikoff SR, Jonas JB, Logan NS, et al (2021) IMI 2021 Reports and Digest – Reflections on the Implications for Clinical Practice. *Invest Ophthalmol Vis Sci* 62(5):1

Wood IC, Hodi S and Morgan L (1995) Longitudinal change of refractive error in infants during the first year of life. *Eye (Lond)* 9(Pt 5):551-557

Wood ICJ, Mutti DO and Zadnik K (1996) Crystalline lens parameters in infancy. *Ophthal Physiol Opt* 16(4):310-317

Woodruff G, Hiscox F, Thompson JR and Smith LK (1994) The presentation of children with amblyopia. *Eye (Lond)* 8(Pt 6):623-626

Xiaoming W, Luxin M and Lihua W (2011) Study on optometry of 1% cyclopentolate cycloplegia in children with hyperopia. Chin J Ophthalmol 47(11):989-994
Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, *et al* (2017) Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol* 95:551-566

Xu L, Cao WF, Wang YX, Chen CX and Jonas JB (2008) Anterior chamber depth and chamber angle and their associations with ocular and general parameters: the Beijing Eye Study. *Am J Ophthalmol* 145:929-936

Yamamoto S, Nitta K and Kamiyama M (1997) Cone electroretinogram to chromatic stimuli in myopic eyes. *Vision Res* 37:2157-2159

Yang HK, Choi JY, Kim DH and Hwang J-M (2014) Changes in Refractive Errors Related to Spectacle Correction of Hyperopia. *PLoS One* 9(11):e110663

Yang Z, Lan W, Ge J, Liu W, Chen X, Chen L, *et al* (2009) The effectiveness of progressive addition lenses on the progression of myopia in Chinese children. *Ophthalmic Physiol Opt* 29:41-48

Yazdani N, Sadeghi R, Momeni-Moghaddam H, Zarifmah-Moudi L and Ehsaei A (2018) Comparison of cyclopentolate versus tropicamide cycloplegia: a systematic review and meta-analysis. *J Optom* 11:135-143

Young FA (1965) The effect of atropine on the development of myopia in monkeys. *Am J Optom Arch Am Acad Optom* 42:439-449

Zadnik K, Manny RE, Yu JA, Mitchell GL, Cotter SA, Quiralte JC, et al (2003) Ocular component data in schoolchildren as a function of age and gender. *Optom Vis Sci* 80(3):226-236

Zhu X, Winawer JA and Wallman J (2003) Potency of myopic defocus in spectacle lens compensation. *Invest Ophthalmol Vis Sci* 44:2818-2827

Zhu X, Park TW, Winawer J et al (2005) In a matter of minutes, the eye can know which way to grow. *Invest Ophthalmol Vis Sci* 46:2238-2241

Zhu X (2013) Temporal integration of visual signals in lens compensation (a review). *Exp Eye Res* 114:69-7

Appendices

Appendix 1

Health Research Authority

West Midlands - Edgbaston Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

28 April 2016

Dr Ian Beasley
Postgraduate student
School of Life and Health Sciences
Aston University
Birmingham
B4 7ET

Dear Dr Beasley

Study title:	**The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes**
REC reference number:	**16/WM/0162**
SSA reference number:	**16/WM/0212**
Protocol number:	**150-2015-IB**
IRAS project ID:	**187441**

The REC gave a favourable ethical opinion to this study on .

Following site-specific assessment by the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s) and investigator(s) listed below:

Research site	*Principal Investigator / Local Collaborator*
School of Life and Health Sciences	Dr Ian Beasley

The favourable opinion is subject to management permission or approval being obtained from the host organisation prior to the start of the study at the site concerned.

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.

16/WM/0162 ***Please quote this number on all correspondence***

Yours sincerely

Adam Garretty
REC Assistant

Email: NRESCommittee.WestMidlands-Edgbaston@nhs.net

Copy to: *N/A Ms Alpa Patel*

NHS
Health Research Authority

West Midlands - Edgbaston Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

28 April 2016

Dr Ian Beasley
Postgraduate student
School of Life and Health Sciences
Aston University
Birmingham
B4 7ET

Dear Dr Beasley

Study title:	**The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes**
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Research site	*Principal Investigator / Local Collaborator*
School of Life and Health Sciences	Dr Ian Beasley

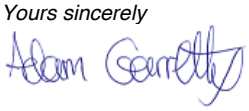
The favourable opinion is subject to management permission or approval being obtained from the host organisation prior to the start of the study at the site concerned.

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.

16/WM/0162	***Please quote this number on all correspondence***

Yours sincerely



Adam Garretty
REC Assistant

Email: NRESCommittee.WestMidlands-Edgbaston@nhs.net

Copy to: *N/A Ms Alpa Patel*

Appendix 2

Aston University

Ian Beasley

School of Life and Health Sciences

Aston Triangle
Birmingham B4 7ET
United Kingdom

Tel: +44 (0)121 204 3000

www.aston.ac.uk

2nd June 2016

Dear Ian

Study title:	The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes.
REC reference:	16/WM/0162
Protocol number:	150-2015-IB
IRAS project ID:	187441
AHRIC ref number:	150-2015-IB
Non-NHS Research Sites:	1. Vision Sciences Aston University. SSA Reference No. 16/WM/0212 2. Eyesite Eyecare Centre, 249 Walsgrave Road, Coventry, CV2 4BA. SSA Reference No. 16/WM/0213

I am writing to confirm permission for your project to proceed on behalf of the University Research Ethics Committee.

This approval is subject to:

- The project being undertaken in conjunction with the non-NHS sites listed above.
- Undertaking the project as described in the Protocol.
- Using the supporting documents listed below.
- Participation of staff and students as described below.
- Formal approval of any amendments including personnel changes.
- Adverse event and serious adverse event reporting.
- Provision of annual reports.
- Provision of End of Study report.
- Provision of study data (anonymised) for archiving.

Amendments to the Project

Any proposed amendments to the project (including personnel) must be approved by AHRIC and if required NHS Research Ethics Committee approval prior to implementation.

Approval of AHRIC should be sought by e-mailing details of the amendment to ahricgovernance@aston.ac.uk.

Adverse Event and Serious Adverse Event Reporting

Appendix 3

Background questionnaire **Date**

Participant code _____

Age _____ years _____months

1. Do you wear glasses?
☐ No (skip to Q4)
☐ Yes
☐ Worn previously but no longer used

2. How old were you when you first started wearing glasses?

_____ years old

3. When do/did you wear your glasses?
☐ Full-time
☐ Concentrated tasks such as TV, computer and reading
☐ Reading only
☐ Distance only
☐ Never
☐ No longer required

4. Have you ever had surgery on your eyes?
☐ No
☐ Yes

If yes, please detail what you had done and when

_____
_____

5. Have you ever been to see a specialist about any other problem with your eyes?
☐ No
☐ Yes

If yes, please detail the reason

_____
_____

6. Have you ever had to wear an eye patch?
☐ No (skip to Q12)
☐ Yes

7. Which eye did you wear the patch on?
☐ Right eye
☐ Left eye

☐ Alternated between eyes

8. How old were you when you started wearing the patch?

_____ years old

9. How old were you when you stopped wearing the patch?

_____ years old

10. How many hours per day were you instructed to wear it?

_____

11. In terms of wearing the patch did you:

☐ Always use it as instructed
☐ Mostly used it as instructed
☐ Hardly used it as instructed
☐ Never used it as instructed

12. Do you suffer from any general health conditions?
☐ No
☐ Yes

If yes, please detail here

_____
_____

13. Are you taking any regular medication?
☐ No
☐ Yes

If yes, please detail here

_____
_____

14. Are you under the care of an eye specialist for any ongoing treatment?
☐ No
☐ Yes

If yes, please detail here

_____
_____

15. Do you wear or have you ever worn contact lenses?
☐ No
☐ Yes

If yes, please detail here

16. Are you participating in any other studies?

☐ No

☐ Yes

Appendix 4

Dear Dr

Re

I am writing to advise you that the above-named patient is participating in a research trial conducted by a team from Aston University. The study will examine the effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes.

Some recent studies have shown that wearing a particular type of contact lens can slow down the progression of myopia. The purpose of this study is to see if a contact lens, similar to those used in the myopia studies, could be used to reduce hyperopia.

The study will last three years with a group of participants wearing the intervention while the other group will have the natural progression of their hyperopia monitored.

I trust that this information is useful but if you require any further information then please contact the investigators.

Yours sincerely

Dr Ian Beasley beasleyi@aston.ac.uk (07798 633536)
Dr Nicola Logan n.s.logan@aston.ac.uk (0121 204 4128)

Appendix 5

CONSENT FORM (Parent natural progression)

NAME OF PARTICIPANT _____ Age: _____ Years _____ Months

Title of Project: The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes

Project investigators: Dr Nicola Logan, Dr Ian Beasley, Dr Leon Davies

Please initial the boxes:

1. I confirm that I have read and understand the information sheet (Version 2 09/05/16) for this study, have had the opportunity to ask questions and have explained the study to my child.	☐
2. I understand that my child's participation is voluntary and that my child is free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐
3. I understand that the researchers may need to review certain sections of my child's eye clinic notes and give my permission for them to do so.	☐
4. I agree for my child to take part in the above study and I will follow the investigator's instructions relating to the dilation drops.	☐

_____ _____ _____

Name of parent/representative Date Signature

_____ _____ _____

Name of person taking consent (If different from investigator) Date Signature

_____ _____ _____

Investigator Date Signature

CONSENT FORM

NAME OF PARTICIPANT _____ Age: _____ Years _____ Months

Title of Project: The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes

Project investigators: Dr Nicola Logan, Dr Ian Beasley, Dr Leon Davies

Please initial the boxes:

1. I confirm that I have read and understand the information sheet (Version 2 07/05/16) for this study, have had the opportunity to ask questions and have explained the study to my child.	☐
2. I understand that my child's participation is voluntary and that my child is free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐
3. I understand that the researchers may need to review certain sections of my child's eye clinic notes and give my permission for them to do so.	☐
4. I agree for my child's GP to be advised about my participation in the study	☐
5. I agree for my child to take part in the above study and I will follow the investigator's instructions relating to contact lens wear and the dilation drops.	☐

_____	_____	_____
Name of parent/representative	Date	Signature
_____	_____	_____
Name of person taking consent (If different from investigator)	Date	Signature
_____	_____	_____
Investigator	Date	Signature

Appendix 6

CONSENT FORM (16-19 Natural progression)

NAME OF PARTICIPANT _____ Age: _____ Years _____ Months

Title of Project: The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes

Project investigators: Dr Nicola Logan Dr Ian Beasley, Dr Leon Davies

Please initial boxes (not tick)

1. I confirm that I have read and understood the information sheet attached (Version 2 07/05/16) for the above study	☐
2. I have had a chance to ask questions about the research.	☐
3. All of my questions have been answered in a way that I understand.	☐
4. I understand that it is my choice on whether or not to take part in the research and that I can stop being part of the research at any time, without giving a reason. The care I receive from my optometrist will not be affected if I ask to be removed from the study.	☐
5. I agree to follow the investigator's instructions regarding the dilation drops.	☐
6. I agree to take part in the study.	☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent (If different from investigator)	Date	Signature
_____	_____	_____
Investigator	Date	Signature

Appendix 7

ASSENT FORM

Participant ID…… **Participant Initials…….**

Title of Project: The effect of peripheral defocus on axial growth and modulation of refractive error in hyperopes

Project investigators: Dr Nicola Logan, Dr Ian Beasley, Dr Leon Davies

(To be completed by the child and their parent/guardian)

Child (or if unable, parent on their behalf) to circle all they agree with:

1. Have you read (or had read to you) the information sheet attached (Version 2 09/05/16) for the above study	*Yes*	*No*
2. Has somebody else explained this project to you?	*Yes*	*No*
3. Do you understand what this project is about?	*Yes*	*No*
4. Have you asked all the questions you want?	*Yes*	*No*
5. Have you had your questions answered in a way you understand?	*Yes*	*No*
6. Do you understand it's OK to stop taking part at any time?	*Yes*	*No*
7. I agree to follow the investigator's instructions regarding contact lens wear and the dilation drops.	*Yes*	*No*
8 Are you happy to take part?	*Yes*	*No*
If any answers are 'no' or you don't want to take part, do not write your name below		

If you do want to take part, you can write your name below

Your name (or if child is unable, parent/guardian to help)	Date	Signature
Name of person taking consent (If different from investigator)	Date	Signature
Investigator	Date	Signature

Thank you for your help.

Appendix 8

Follow up questionnaire **Date**

Participant code _____

Age _____ years _____months

1. Do you suffer from any general health conditions?

☐ No
☐ Yes

If yes, please detail here

_____
_____

2. Are you taking any regular medication?

☐ No
☐ Yes

If yes, please detail here

_____
_____

3. Are you under the care of an eye specialist for any ongoing treatment?

☐ No
☐ Yes

If yes, please detail here

_____
_____

4. How many days per week are you wearing your contact lenses?

_____

5. On average, how many hours per day are you wearing your contact lenses?

_____

6. Is the vision clear with your contact lenses?

☐ No
☐ Yes

Follow up questionnaire **Date**

Participant code _____

Age _____ years _____months

1. Do you suffer from any general health conditions?

☐ No

☐ Yes

If yes, please detail here

_____
_____

2. Are you taking any regular medication?

☐ No

☐ Yes

If yes, please detail here

_____
_____

3. Are you under the care of an eye specialist for any ongoing treatment?

☐ No

☐ Yes

If yes, please detail here

Appendix 9

Aston University
Aston Triangle
Birmingham
B4 7ET
0121 204 5069

Date: 12th February 2019

Dr Ian Beasley
School of Life and Health Sciences

Dear Ian,

Study title:	Time course and repeatability of objective refraction and axial length measures following cycloplegia
REC REF:	#1331

Confirmation of Ethical Opinion

On behalf of the Committee, I am pleased to confirm a favourable opinion for the above research based on the basis described in the application form, protocol and supporting documentation listed below.

The Committee would like to thank you for the way that your response to their letter of Provisional Opinion was presented.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Parent Information Sheet	2	21/01/19
Parent Consent Form	2	21/01/19
Information Sheet (8-12)	2	21/01/19
Assent form (8-12)	2	21/01/19
Information Sheet (13+)	2	21/01/19
Consent form (13+)	2	21/01/19
Recruitment poster		
Background questionnaire	2	25/11/18

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

Yours sincerely

Professor Richard Booth
Acting Chair of the University Research Ethics Committee

Appendix 10

Background questionnaire **Date**

Participant code _____

Age _____ years

1. Do you wear glasses?
☐ No (skip to Q3)
☐ Yes
☐ Worn previously but no longer used

2. When do/did you wear your glasses?
☐ Full-time
☐ Concentrated tasks such as TV, computer and reading
☐ Reading only
☐ Distance only
☐ Never

3. Have you ever had surgery (including laser treatment) on your eyes?
☐ No
☐ Yes

If yes, please detail what you had done and when

_____
_____

5. Have you ever been to see a specialist about any other problem with your eyes?
☐ No
☐ Yes

If yes, please detail the reason

_____
_____

6. Do you suffer from any general health conditions?
☐ No
☐ Yes

If yes, please detail here

_____
_____

7. Are you taking any regular medication?
☐ No
☐ Yes

If yes, please detail here

_____

_____

8. Are you under the care of an eye specialist for any ongoing treatment?

☐ No

☐ Yes

If yes, please detail here

Appendix 11

Time course and repeatability of objective refraction and axial length measures following cycloplegia

Parent consent Form

Name of Chief Investigator: Dr Ian Beasley

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (Version 3, 03/04/19) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my child's participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	
3.	I agree to my child's personal data and data relating to them collected during the study being processed as described in the Participant Information Sheet.	
4.	I agree to my child's GP being informed of my participation in the study.	
5.	I agree to my child's anonymised data being used by research teams for future research.	
6.	I agree to my child's personal data being processed for the purposes of inviting them to participate in future research projects. I understand that I may opt out of receiving these invitations at any time.	
7.	I agree to my child taking part in this study.	

Name of parent	Date	Signature
Name of Person receiving consent.	Date	Signature

Appendix 12

Time course and repeatability of objective refraction and axial length measures following cycloplegia

Consent Form

Name of Chief Investigator: Dr Ian Beasley

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (Version 3, 03/04/19) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	
3.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
4.	I agree to my GP being informed of my participation in the study.	
5.	I agree to my anonymised data being used by research teams for future research.	
6.	I agree to my personal data being processed for the purposes of inviting me to participate in future research projects. I understand that I may opt out of receiving these invitations at any time.	
7.	I agree to take part in this study.	

Name of participant	Date	Signature
Name of Person receiving consent.	Date	Signature

Appendix 13

Time course and repeatability of objective refraction and axial length measures following cycloplegia

Assent form

Name of Chief Investigator: Dr Ian Beasley

(To be completed by the child and their parent/guardian)

Child to circle all they agree with:

2. Have you read (or had read to you) the information sheet attached (Version 3 03/04/19) for the above study	*Yes*	*No*
2. Has somebody else explained this project to you?	*Yes*	*No*
3. Do you understand what this project is about?	*Yes*	*No*
4. Have you asked all the questions you want?	*Yes*	*No*
5. Have you had your questions answered in a way you understand?	*Yes*	*No*
6. Do you understand it's OK to stop taking part at any time?	*Yes*	*No*
7. I agree to follow the investigator's instructions regarding the dilation drops.	*Yes*	*No*
8. Are you happy to take part?	*Yes*	*No*
If any answers are 'no' or you don't want to take part, do not write your name below		

If you do want to take part, you can write your name below

_____

Your name Date Signature

_____

Name of Person receiving consent. Date Signature

Appendix 14

	Intervention group		
Participant	**Age at baseline** (years)	**MSE refractive error at baseline** (D)	**Change in AL** (mm)
1	9.58	+2.62	0.59
2	13.50	+2.94	0.21
3	11.83	+4.45	0.05
4	9.25	+8.75	0.06
5	13.33	+6.13	0.02
6	9.67	+3.87	0.36
7	11.08	+5.74	0.29
8	11.83	+7.63	0.07
9	8.42	+8.12	0.18
10	11.17	+4.98	0.33
11	12.75	+2.37	0.11

Appendix 14 Individual participant data for intervention group showing key characteristics. Rows shaded in orange highlight the two best responders whereas the rows shaded in red highlight the worst responders

Supporting publications

Beasley IG, Davies LN and Logan NL (2018) Effect of Peripheral Defocus on Axial Eye Growth and Modulation of Refractive Error in Hyperopes: Protocol for a Nonrandomized Clinical Trial. *JMIR Res Protoc* 7(9):e173

Beasley IG, Davies LN and Logan NL (2019) The effect of peripheral defocus on axial growth in hyperopes. *Invest Ophthalmol Vis Sci* 60:5829