Long-term impact of a myopia control contact lens on myopia progression and ocular health of young myopic eyes.

Paul Chamberlain

Doctor of Philosophy

ASTON UNIVERSITY

March 2025

Aston University

Long-term impact of a myopia control contact lens on myopia progression and ocular health of young myopic eyes.

Paul Chamberlain

Doctor of Philosophy

2025

Abstract

Myopia, characterized by the inability to focus light from distant targets due to the elongation of the posterior eyeball, results in blurred vision. The global prevalence of myopia has surged, particularly in East and Southeast Asia, where rates approach 100% in young urban populations. Structural changes in the posterior eye associated with elongation can lead to sight-threatening pathologies such as myopic maculopathy, a special concern for high myopias (SE<-6.00D).

Research has focused on understanding myopia onset and progression and developing interventions to slow its progression. Studies in non-human primates have shown that hyperopic defocus accelerates eye growth, while myopic defocus can retard this growth. Dual focus optics, which introduce myopic defocus, have been effective in animal models and inspired the development of MiSight, a dual focus contact lens designed to slow myopia progression.

Assessing efficacy of myopia control treatments is complex due to varied visual environments and the need for long-term monitoring to provide evidence of sustained effectiveness. Concerns about the long-term sustainability of initial myopia control effects and the safety of daily full-time contact lens wear in young children necessitated comprehensive clinical trials to assess both efficacy and safety. The MiSight study, a multi-year, multi-center clinical trial was designed to meet this need. This thesis is based upon seven publications that examine the ability of a dual focus contact lenses to safely slow myopia progression. Chapters explore the challenges of assessing treatment efficacy while quantifying risks of long-term contact lens wear in children. Different approaches for assessing efficacy are explored, along with efforts to quantify the treatment "dose" delivered to the retina.

This work has shown that a contact lens intervention based on the principle of delivering myopic defocus to the retina can sustain slowed eye growth for multiple years in safe and effective manner.

Keywords: axial length, contact lenses, emmetropic eye growth, myopia, myopia control, myopia progression, refractive error

Dedication

For my family

Acknowledgements

To begin, I would like to recognize all my professional friends and colleagues: You have been an integral part of my academic and professional life. Each of you has contributed to my growth in unique ways—through collaboration, insightful discussions, shared challenges, or moments of encouragement. The knowledge, support, and camaraderie I have gained from working alongside you have been invaluable. Thank you for challenging me and helping me become a better thinker and researcher. From my early years as a dispensing optician in Hereford to the present time leading a research group in California, each of you has shaped a passion that powered me on this part of my professional journey.

The MiSight study, which forms the spine of this research, would not have happened without the dedication of past and present colleagues at CooperVision, the clinical sites, Visioncare Research, and of course, the children and their families who dedicated so much of their time and trust to take part in this project.

For this thesis, I want to particularly acknowledge Nicola Logan, my mentor for this project, who went above and beyond to convince me to embark on this writing journey, which has given me so much satisfaction. Also, to Arthur Bradley for giving me guidance and encouragement throughout this writing process.

Finally, I want to send my love to my family: My parents, who instilled in me the value of education, perseverance, and integrity. To my wife and family, for your patience and understanding over the past year. Writing this thesis has been rewarding but demanding, and I am deeply grateful for your support.

This work is a testament to the guidance and support of those around me. Thank you all for being part of this journey.

Author Contribution

Paper 1. Chapter 3. Section 3.3

A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control. Optometry and Vision Science 96(8):p 556-567, August 2019.

Conceptualization: PC, NSL; Formal Analysis: PC, GY; Investigation: SCP-d-M, NSL, CN, DJ; Project Administration: PC, GY; Writing – Original Draft: PC; Writing – Review & Editing: PC, SCP-d-M, NSL, CN, DJ, GY.

Paper 2. Chapter 4. Section 4.2

Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial. Optometry and Vision Science 99(3):p 204-212, March 2022.

Conceptualization: PC, JM, GY; Data Curation: CH; Formal Analysis: PC, AB, BA, DH, JM, CH, GY; Investigation: NSL, DJ, CN, SCP-d-M; Project Administration: PC, JM, GY; Validation: CH; Writing – Original Draft: PC, AB; Writing – Review & Editing: PC, AB, BA, DH, JM, NSL, DJ, CN, SCP-d-M, CH, GY.

Paper 3. Chapter 5. Section 5.2

Ocular health of children wearing daily disposable contact lenses over a 6-year period. Cont Lens Anterior Eye. 2021 Aug;44(4):101391.

Paul Chamberlain contribution was confirmed as part of the application process by the first author of the paper in a signed declaration dated March 15, 2023, in the absence of a formal CRedIT taxonomy in this journal. The contribution was as follows:

Conceptualization (Equal), Formal analysis (Equal), Methodology (Equal), Project Admininistration (Equal), Resources (Equal), Supervision (Equal), Validation (Equal), Visualization (Equal), Writing – original draft (Support), Writing – review and editing (Equal)

Paper 4. Chapter 5. Section 5.3

Adverse event rates in the retrospective cohort study of safety of paediatric soft contact lens wear: the ReCSS study. Ophthalmic Physiol Opt. 2021 Jan;41(1):84-92.

Robin L Chalmers: Conceptualization (equal); Data curation (lead); Investigation (lead); Methodology (equal); Project administration (lead); Writing-original draft (lead); Writing-review & editing (equal). John J McNally: Conceptualization (equal); Funding acquisition (lead); Methodology (equal); Writing-original draft (supporting); Writing-review & editing (equal). Paul Chamberlain: Conceptualization (equal); Funding acquisition (lead); Investigation (supporting); Methodology (equal); Writing-original draft (supporting); Writing-review & editing (equal). Lisa Keay: Formal analysis (equal); Methodology (equal); Writing-original draft (supporting); Writing-review & editing (supporting).

Paper 5. Chapter 6. Section 6.4

Axial length targets for myopia control. Ophthalmic Physiol Opt. 2021 May;41(3):523-531.

Paul Chamberlain: Conceptualization (equal); Data curation (equal); Investigation (equal); Writing-review & editing (equal). Percy Lazon: Writing-review & editing (equal). Baskar Arumugam: Writing-review & editing (equal). Mark Bullimore: Formal analysis (equal); Methodology (equal); Writing-original draft (lead).

Paper 6. Chapter 6. Section 6.5

Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial. Optom Vis Sci. 2022;99(3):204-212.

Paul Chamberlain: Conceptualization-Equal, Investigation-Equal, Methodology-Equal, Project administration-Equal, Supervision-Equal, Visualization-Equal, Writing – original draft-Lead, Writing – review & editing-Equal; David Hammond: Conceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Methodology-Equal, Validation-Equal, Visualization-Equal, Writing – original draft-Supporting, Writing – review & editing-Equal; Baskar Arumugam: Conceptualization-Equal, Investigation-Equal, Methodology-Equal, Resources-Equal, Validation-Equal, Visualization-Equal, Writing – original draft-Supporting, Writing – review & editing-Equal; Arthur Bradley: Conceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Methodology-Equal, Supervision-Lead, Writing – original draft-Lead, Writing – review & editing-Equal

Paper 7. Chapter 7. Section 7.3

Myopia Control Dose Delivered to Treated Eyes by a Dual-focus Myopia-control Contact Lens. Optometry and Vision Science 100(6):p 376-387, June 2023.

Conceptualization: VR, NSL, DM, PC, BA, AB, PSK; Data Curation: VR; Formal Analysis: VR, DM, MJ, MR, PC, BA, AB, PSK; Investigation: VR, NSL, SJ, PC, BA, AB, PSK; Methodology: VR, DM, MJ, MR, PC, BA, AB, PSK; Project Administration: NSL, SJ, PC, BA, AB, PSK; Resources: NSL, SJ, AB, PSK; Software: VR, MJ, MR; Supervision: NSL, PC, BA, AB, PSK; Validation: VR; Visualization: VR, DM, AB, PSK; Writing – Original Draft: VR, AB; Writing – Review & Editing: VR, NSL, DM, MJ, MR, PC, BA, AB, PSK.

Table of Contents

List of Tables

List of Figures

CHAPTER 1:INTRODUCTION

1.1. Pathological eye growth, myopia development and the motivation to intervene

Myopia is characterized by an inability to focus light from distance targets because the optical components of the eye focus light rays in front of, rather than on, the retina, resulting in a blurred image and an accompanying visual disability. Although historically corrected with optical appliances and considered by many to be an optical anomaly and a benign condition, myopia is not typically produced by excessive power in the eye's optics, but rather by excessive growth of the posterior eye. This excessive elongation of the posterior eye can result in sight threatening pathological complications later in life. The most commonly recognized consequence being myopic maculopathy. (Hayashi, Ohno-Matsui et al. 2010) More recently evidence has been assembled to relate the presence of Myopia as a risk factor for Cataract, Glaucoma and Retinal Detachment. (Flitcroft 2012)

Due to a dramatic increase in myopia prevalence globally, (Holden, Fricke et al. 2016, Rudnicka, Kapetanakis et al. 2016) it is now considered a significant global public health concern. A report co-produced by the World Health Organization and Brien Holden Vision Institute outlined critical areas of future focus for this issue. (Mariotti, Kocur et al. 2015) Of particular concern are recent estimates from East and Southeast Asia indicating myopia prevalence rates nearing 100% in young urban populations. (Lin, Shih et al. 2004, Jung, Lee et al. 2012) Equally concerning is the significant increase in high myopia prevalence, classified as myopia greater than 6.00D (Lin, Shih et al. 2004) (Tsai, Liu et al. 2021) due to the greatly increased risk of sight threatening pathology associated with high myopias. (Flitcroft 2012) The picture in the rest of the world is similarly concerning, with studies in the USA (Vitale, Ellwein et al. 2008) and United Kingdom (McCullough, O'Donoghue et al. 2016) showing increased myopia prevalence over the last few decades. This rising prevalence is appearing in tandem with evidence of onset of myopia at younger ages, (Fan, Lai et al. 2011) and earlier onset is highly correlated with a greater final level of myopia and hence an associated increased risk of retinal pathologies later in life. (Chua, Sabanayagam et al. 2016, Verkicharla, Kammari et al. 2020) Reports on the incidence of rhegmatogenous retinal detachment show an increase in prevalence in younger eyes contrasting with the typical appearance later in life. (Park, Choi et al. 2013) These factors combine to create an alarming prediction of future associated retinal diseases and untreatable vision loss in millions of individuals, particularly in East Asia. (Verkicharla, Ohno-Matsui et al. 2015)

Although risks of pathology are much higher in highly myopic eyes, it should not be assumed that the situation only reaches a concerning level once meeting the somewhat arbitrary stated threshold of spherical equivalent refractive errors of more than -6.00D. Flitcroft in a seminal paper (Flitcroft 2012) stated "there is no safe level of myopia". The relationship between increasing levels of myopia and increased likelihood of sight threatening vision problems is well established, with each increasing diopter of myopia associated with a 67% increase in the prevalence of myopic maculopathy. (Bullimore and Brennan 2019) Due to the far greater numbers of myopes with refractive impairment less than 6 diopters of myopia, there are a large population of patients at risk with of later pathologies who have so called "physiological myopia". Flitcroft emphasizes that this label incorrectly implies that lower levels of myopia are not associated with pathology. In fact, observations from the Blue Mountains eye study in Australia established that over 40% of the myopia maculopathy cases were recorded in patients with Myopia less than 5.00D. (Vongphanit, Mitchell et al. 2002)

Therefore, the potential value of a treatment that slows myopia progression is its ability to reduce the prevalence of higher myopias and hence lower the likelihood of myopic eyes experiencing pathologies later in life. Bullimore calculated that reducing myopia levels by 1D would create a 40% reduction in the risk of suffering maculopathy. (Bullimore and Brennan

2019) These calculations highlight a disease continuum (Flitcroft 2012, Brennan 2015) in which any excessive growth in the posterior eye places the eye at risk of damage later in life. However, proof that slowed progression as a result of treatment in a young eye will ultimately lower the risk of pathology when that eye ages may take decades to establish. Nevertheless, one cannot ignore the association between myopia level and visual impairment. In 2015, estimates detailed 3.3 million people were blind due to myopia, (Fricke, Jong et al. 2018) this prevalence rises to 18.5 million by 2025, assuming the same relationship to myopia level. Thus, the reality for the eyecare community would be that waiting for evidence of lower pathology through myopia control interventions study, would leave a staggering amount of the global population blind or visually impaired. Despite this uncertainty, the appetite to arrest this condition through some sort of “myopia control” intervention is increasing steadily. (Efron, Morgan et al. 2020)

Most evidence points to the modern environment experienced by children as the underlying trigger for the dramatic acceleration of eye growth and the accompanying increase in myopia prevalence. (Wolffsohn, Flitcroft et al. 2019) These environmental changes will modify the retinal image. (Flitcroft 2012) Experimental studies of non-human primates and other animals have shown that altering the retinal image can accelerate or retard eye growth.(Wallman and Winawer 2004) Early studies (Wiesel and Raviola 1977) of monkeys showed that eye growth could be accelerated by lowering retinal image contrast, and later studies in several species showed that eye growth could be adjusted to place the retina coincident with the retinal image plane. (Schaeffel, Glasser et al. 1988, Hung, Crawford et al. 1995, Shaikh, Siegwart et al. 1999, Smith and Hung 1999, Wildsoet and Schmid 2001, Howlett and McFadden 2009)

The shift from outdoor to predominantly indoor lifestyles of the modern child is suspected to be a significant driver of increased myopia prevalence. The growing emphasis on education globally, is a driving force for the dominant indoor experience of modern children. (Mountjoy, Davies et al. 2018) (Mirshahi, Ponto et al. 2014) Countries and regions with higher educational pressures at an earlier age in particular exhibit higher prevalences of myopia. (Morgan and Rose 2013) Conversely, other research has shown that children who spend more time outdoors and less time with near viewing exhibit a lower risk of developing myopia compared with children with low outdoor time and high reported daily hours of near work. (Rose, Morgan et al. 2008) Critically, the indoor environment exhibits significantly lower levels of light, typically 100-500 lux, (Norton and Siegwart 2013) contrasting with outdoor levels of up to 130000 lux on a bright sunny day and even 15000 lux in a shaded environment. Also, because of the needs for efficiency, and the low visual sensitivity to very short wavelengths, indoor lighting also lacks the shortest visible wavelengths (e.g. below 420 nm) and UV radiation. Although lacking convincing data, it has been hypothesized that eye growth regulation and normal eye size requires these very short wavelengths to be present in the environmental spectrum. (Torii, Kurihara et al. 2017, Mori, Torii et al. 2021)

Whilst indoors, children spend more time focusing on near targets. (Dahlmann-Noor, Bokre et al. 2025) To focus on near targets, children must accommodate, but due to accommodative lag, which can be larger in myopic children (Mutti, Mitchell et al. 2006) image planes will likely be located posterior to the retina. Since experimentally created hyperopic defocus (negative lens rearing) leads to accelerated eye growth and resulting myopia in animals, (Wildsoet and Wallman 1995, Smith and Hung 1999) it is possible that chronic hyperopic defocus generated by indoor near viewing and accommodative lags can be the driver for accelerated eye to grow in humans, creating myopia. It has been suggested, therefore, that the accelerated eye growth that causes myopia is an adaptation to the modern environment, and not a failure of the eye growth regulation mechanisms.

Accelerated eye growth associated with hyperopic defocus of retinal images in infant monkeys can be prevented when some myopically defocused light is presented simultaneously. The animal studies showed that chickens and monkeys reared with negative lenses could be prevented from developing myopia by inclusion of some relatively positive power somewhere

in the optical path. (Tse, Lam et al. 2007, Liu and Wildsoet 2011, Liu and Wildsoet 2012, Arumugam, Hung et al. 2014, McFadden, Tse et al. 2014, Arumugam, Hung et al. 2016) If two focal planes are present, the eye will grow to focus the least hyperopic focal plane (the one that requires least growth to focus). These dual focus experiments led to the hypothesis that adding some myopically defocused light (image plane anterior to the retina) could counteract the grow signal generated by accommodative lags and prevent the acceleration of eye growth.

These results highlight an exciting possibility: The chronic exposure to the myopigenic environment of the modern world can be mitigated by delivering myopic defocus to the retina of progressing myopic children. In order to be clinically valuable, ophthalmic lenses must simultaneously include both the optical power required to create myopic defocus and the optics necessary to correct the refractive anomaly of the wearer (and improve vision). One such dual focus strategy implemented in a contact lens (CL) employs a distance correction to focus some or most of the light at the retina and some concentric annular zones with added plus power. This strategy has been included in the design of the dual focus CL studied in this thesis. (Anstice and Phillips 2011)

1.2. Slowing accelerated eye growth in myopic eyes

For many years, under correction in juvenile onset myopia was employed in an attempt to slow the subsequent progression. Anecdotal reports suggest that this approach aimed to reduce the accommodative demand during near tasks in this age group and thus reduce accommodative lags. However, subsequent trials have failed to support this hypothesis, (Adler and Millodot 2006, Koomson, Amedo et al. 2016) and one study even showed greater progression in under-corrected myopic eyes. (Chung, Mohidin et al. 2002) Such studies are challenging to implement due to the inevitable associated lifestyle and thus potentially retinal image changes that likely accompany under-correction. Uncorrected or under-corrected myopic children will not have focused retinal images when viewing distant targets but may have well-focused images when viewing near targets, and therefore such interventions to slow myopia progression have the potential to increase myopia progression by biasing the child's behavior in favor of near viewing in the indoor environment.

Repurposing of presbyopic spectacle lens designs to control myopia has had a limited effect on myopia progression. Presbyopic spectacles included bifocals, and multifocal lenses have been explored as myopia control devices. (Pärssinen, Hemminki et al. 1989, Fulk, Cyert et al. 2000, Edwards, Li et al. 2002, Gwiazda, Hyman et al. 2003, COMET 2 Study Group 2011, Berntsen, Sinnott et al. 2012, Cheng, Woo et al. 2014) Employing presbyopic spectacles were thought to reduce accommodative lag and any associated hyperopic defocus, and the nature of the optical design would also result in myopic defocus in the superior peripheral retina for many near viewing conditions. However, during the 1980's the "Houston Myopia Study" recruited subjects between the ages of 6-15 to be randomized to receive either single vision spectacles, bifocal spectacles with +1.00D or +2.00D of addition. Following three years of observation there was no statistical or clinically significant difference in myopia progression. (Grosvenor, Perrigin et al. 1987) A larger 3 year study using Progressive Addition Lenses (PAL) observed only a 0.2D slowing of myopia progression in US children.(Gwiazda, Hyman et al. 2003) Slightly greater slowing was observed in children exhibiting accommodative lag and esophoria, which prompted a follow on study, which again observed clinically insignificant slowing of myopia progression. (COMET 2 Study Group 2011) More promising results were observed using executive bifocal type design, with one intervention arm also including a 3Δ Base In prism. (Cheng, Woo et al. 2014) This latter group showed a 50% slowing over 3 years, but this result has not been replicated. Lenses with a peripheral myopic defocus, not specifically targeted at presbyopic correction was also found to only result in modest effects. (Sankaridurg, Donovan et al. 2010)

Newer spectacle designs have emerged that specifically target myopia control. (Lam, Tang et al. 2019, Bao, Huang et al. 2022, Bao, Yang et al. 2022, Lam, Tang et al. 2022, Lam, Tang et

al. 2023, Chen, Wu et al. 2024) Each of these designs include small “lenslets” to deliver additional positive power through some proportion of the spectacle lens to mitigate any myopigenic stimuli reaching the retina. Effective slowing of myopia progression has been achieved by all three of these dual focus spectacle lens designs. Also, a recent study from the group at Wenzhou found that dual focus spectacle lenses with small lenslets containing either added plus or added minus power both slowed myopia progression and axial elongation. The secondary focal planes defined by the lenslet local curvatures generated by the added plus and added minus zones are very different, but because the lenslets employed in the Wenzhou study employed a non-coaxial design all optical beams converge toward each other and approximately superimpose around the base optical focal plane the resulting retinal blur and contrast reduction created are similar for these two designs. (Su, Cho et al. 2024)

Overnight orthokeratology involves overnight wear of a rigid contact lens that flattens the central cornea to reduce the optical power of a myopic eye sufficiently to place the optical image plane coincident with the retinal plane. Upon wakening, the central corneal flattening achieves approximate emmetropia, with the peripheral optics creating myopic defocus. Due to the nature of orthokeratology, the impact of OK on myopia progression cannot easily be ascertained by monitoring changes in refractive state, and therefore, any myopic control effect must be assessed by differences of axial elongation. Several trials have explored controlling myopia via this intervention. (Cho, Cheung et al. 2005, Walline, Jones et al. 2009, Cho and Cheung 2012, Hiraoka, Kakita et al. 2012, Santodomingo-Rubido, Villa-Collar et al. 2012, Charm and Cho 2013, Chen, Cheung et al. 2013, Swarbrick, Alharbi et al. 2015, Kakita, Hiraoka et al. 2016, Li, Kang et al. 2016) A meta-analysis reviewing all studies utilizing this technique estimated an effect (slower growth than seen in untreated control eyes) of approximately 0.14mm per year, supporting that this type of intervention is a viable mechanism to achieve myopia control. (Li, Kang et al. 2016) Because the range of myopia that OK can correct is limited, it cannot be applied universally to all myopias. (Charm and Cho 2013) There is currently no available strategies for controlling the magnitude of myopic defocus present in the OK-treated peripheral cornea, and it is this peripheral region which creates myopic defocus that is the likely refractive property responsible for reducing the myopia progression rates.

Early efforts to use soft multifocal or bifocal contact lenses for myopia control also utilized existing designs developed for Presbyopia. Designs that generally contain optics with additional positive power. (Walline, Greiner et al. 2013, Aller, Liu et al. 2016) The short-term investigations showed promise in slowing myopia progression by 50% or more. The initial work with lenses designed to correct presbyopia, was continued with longer term studies, also showing a strong effect. (Walline, Walker et al. 2020) A contact lens design specifically targeted for myopia control employed a dual focus design (the precursor of the MiSight® lens (CooperVision Inc.) and was tested in a unique contralateral eye design, treating each eye separately in a cross-over design (10 months per condition). (Anstice and Phillips 2011) Results were positive with 50% slowing observed for the test intervention. A study using lens designs developed at Hong Kong Polytechnic University, with multiple alternating zones of correction and myopic defocus, demonstrated modest slowing. (Lam, Tang et al. 2014) The Hong Kong study suffered from significant noncompliance and dropout, a result which suggested that full time wear may be a critical component of a successful myopia control intervention. Slightly less slowing was also observed in another design specifically developed for myopia control utilizing myopic defocus through multifocality, studied over 12 months. (Sankaridurg, Holden et al. 2011) The same group later developed further novel designs, still utilizing myopic defocus, but ostensibly targeting an “extended depth of focus” target. The designs achieved slowing of slightly less than 50%, but again with an uncertain impact of significant dropout and noncompliance to wear time in the test interventions. (Sankaridurg, Bakaraju et al. 2019) Further novel soft contact lens designs have also been assessed with some level of success. (Garcia-Del Valle, Blázquez et al. 2021)

Most dual focus and multifocal optics introduce two changes to the optical environment of the retina. In addition to establishing a second (or multiple) focal plane(s) anterior to the retina with plus power, the sum of the defocus and focused images result in lower image contrast that present with a fully focused (single vision) image. A unique myopia control spectacle lens design includes scatter optics that do not create a second focal plane, but do lower image contrast. (Neitz and Neitz 2024) A clinical trial of this approach, showed significant slowing in myopia progression and axial elongation in the first year, (Rappon, Chung et al. 2023) but more modest gains in subsequent years, that may have resulted from uncertain impacts of the COVID-19 pandemic.(Laughton, Hill et al. 2024) The early promise and failure to observe a treatment effect in years 2 and 3 emphasize the importance of validating efficacy over multiple years.

1.3. Challenges of assessing efficacy of a myopia control therapy

Assessing the efficacy of a myopia control treatment in a human patient population is challenging because (1) the study cannot control the visual environments experienced by children; (2) the relatively slow progression of myopia in western countries (e.g. 0.25D to 0.50D /year;(Donovan, Sankaridurg et al. 2012) and (3) possible confounding of treatment effects with progression changes unrelated to treatment. (Brennan and Cheng 2019, Brennan, Toubouti et al. 2020) Therefore, to average out environmental variance (Goss and Rainey 1998, Fulk, Cyert et al. 2002) and to create a measurably large axial growth and myopia progression signal, assessing myopia control efficacy requires long-term measurement and large sample sizes. (Walline, Robboy et al. 2018, Wolffsohn, Kollbaum et al. 2019) Robust randomization and masking are essential to minimize bias that could impact the study results. Therefore, rigorous randomized clinical trials try to match control and treatment cohorts with sample sizes adequate to detect treatment effects are required. (Lawrenson, Shah et al. 2023)

Further consideration must be given to the time course of the myopia condition, when designing trials. Multiple population based-studies have provided evidence via prevalence estimates that myopia onset can occur at ages as young as 5 in white European/North American populations (Rudnicka, Kapetanakis et al. 2016, Theophanous, Modjtahedi et al. 2018, Tricard, Marillet et al. 2022) Onsets at even younger ages have been observed in Asian populations. (Ma, Qu et al. 2016, Rudnicka, Kapetanakis et al. 2016) Once myopia has developed, myopia continues progress over multiple years. (Goss and Cox 1985, Jones, Mitchell et al. 2005, Wong, Machin et al. 2010, Donovan, Sankaridurg et al. 2012, Xiang, He et al. 2012, Pärssinen, Kauppinen et al. 2014, McCullough, O'Donoghue et al. 2016, Jones-Jordan, Sinnott et al. 2021, Qin, Peng et al. 2022) Therefore, although prevalence of myopia is generally low in younger children (e.g. 2% in White and 6% in Asian at age 5) the population prevalence increases steadily up to adulthood. (Rudnicka, Kapetanakis et al. 2016) In white populations 77% of myopias have stabilized (no more progression) by age 18, (Hardy, Hillis et al. 2013) but some myopias progress after age 18. (Hardy, Hillis et al. 2013, Pärssinen, Kauppinen et al. 2014, Bullimore, Lee et al. 2023) Estimates of myopia progression over this time period vary significantly between individuals (Brennan, Shamp et al. 2024) and across populations. (Rudnicka, Kapetanakis et al. 2016) This younger onset in Asia results in greater prevalence of higher myopia than typically observed in a western population and creates a concerning picture for the levels of myopia at stabilization given the age at stabilization and faster myopia progression in younger ages. (Chua, Sabanayagam et al. 2016) (Jones-Jordan, Sinnott et al. 2021) Because faster myopia progression is observed in the years immediately before and just following the age when refractive myopia is first detected clinically (Mutti, Hayes et al. 2007) and are generally faster in the younger eyes,(Chua, Sabanayagam et al. 2016, Jones-Jordan, Sinnott et al. 2021) sustained interventions at younger ages when the disease is most aggressive is likely to produce the greatest long term clinical value. Further, because the accelerated eye growth underlying myopia can happen over many years from early childhood to young adulthood, a clinical trial must identify a targeted age range, and most studies recruit subjects between ages 8 and 12. (Walline, Robboy et al. 2018, Wolffsohn, Kollbaum et al. 2019)

Implementing a myopia control treatment utilizing contact lenses faces an additional challenge. There has long been concern that contact lenses are not a safe ophthalmic correction for children. (Walline, Robboy et al. 2018) Even when contact lenses are prescribed for children, there has been a tendency to recommend part time wear, either in the form of fewer hours per day or limited days per week, presumably on the basis that this could limit the risk of common contact lens adverse events. However, some study results have suggested that part time wear of myopia control interventions may result in lessening treatment effect in the primary goal of reducing myopia progression. (Lam, Tang et al. 2014, Sankaridurg, Bakaraju et al. 2019, Bao, Huang et al. 2022) Fortunately, with the increased interest and prevalence of studies for contact lens wear in myopic children, longitudinal and retrospective studies have provided evidence that contact lenses are indeed a safe and effective vision correction for the younger wearer. (Dias, Manny et al. 2013, Plowright, Maldonado-Codina et al. 2015, Bullimore 2017) Because of the relative paucity of safety data for children wearing soft contact lenses, the myopia control study described in this thesis offered an opportunity to assess any corneal changes associated with sustained long-term wear of soft contact lenses. The study monitored ocular health over 6 years of contact lens treatment, which was followed by a retrospective chart review seeking evidence of the rate of microbial keratitis in children fit with contact lenses.

Achieving full time wear in a contact lens intervention also requires an optical correction that provides high quality vision in challenging and varying visual requirements of a population whose lifestyle and visual needs develop as they mature. In summary, an effective ophthalmic myopia control intervention must deliver sufficiently high-quality vision over multiple years to ensure compliance. Prior to the MiSight 1 day contact lens study that forms the basis for this PhD, a limited number of soft contact lens interventions had evaluated their impact beyond one year of treatment. (Walline, Greiner et al. 2013, Lam, Tang et al. 2014) The 6-year myopia control trial of the MiSight contact lens was designed to (1) assess efficacy (can this dual focus contact lens slow or stop myopia progression?); (2) Does the added myopia control optics impact quality of life? (3) Can children wear daily disposable soft CLs for >10 hours per day for 6 days per week without experiencing high levels of anterior eye problems?; and (4) can treatment efficacy be sustained over time scales required to cover the natural history of accelerated myopic eye growth?

CHAPTER 2: OPTICAL DESIGN OF THE MISIGHT DUAL-FOCUS MYOPIA CONTROL CONTACT LENS

2.1. Background to the dual focus design

Unlike a traditional “single vision” contact lens which has a single optical function to generate focused images at the retina, the goal of an optical myopia control intervention is to both provide good acuity by the correction of refractive error, the ‘distance correction’ optic, and also to include an optic designed to slow or stop the accelerated eye growth associated with progressive myopia. Such dual function contact lenses must be compatible with full time wear and provide seamless integration with the visual and lifestyle demands of a young population. The specific design studied in this thesis is based upon the hypothesis that adding significant myopic defocus to the retinal image will slow the progression of myopia and accompanying axial elongation.

Soft contact lens geometries have been optimized over many years and modern designs offer predictable optical corrections with high levels of biocompatibility when they locate on the surface of the avascular cornea. (Maldonado-Codina 2024, Young 2024) Modern lens designs have been shown to perform in a wide range of eyes and for the majority of refractive errors. (Dumbleton, Chalmers et al. 2002, Hickson-Curran, Young et al. 2016) Stable contact lens centration across the cornea, confirmed with assessment of limbal overlap provides approximate centration over the pupil for rays forming the foveal image crucial for good distance vision. Decentrations relative to the primary line of sight are common but generally fractions of a mm. (Walther, Meyer et al. 2024) A stable lens position ensures that the optics delivered to the retina (distance correction and myopia control signals) remain somewhat consistent for different patients and throughout daily wear. However, other important considerations cannot be overlooked. Whereas, we might be able to ensure that the geometrical positions of the designed optics remain relatively consistent to the pupil and the foveal-relevant primary line of sight during regular wear, the pupil can vary in size over a wide range, and vary between individuals. (Winn, Whitaker et al. 1994) Environmental factors that control pupil size in an individual include light level, spectral composition of light, and accommodation status. (Kasthurirangan and Glasser 2005, Watson and Yellott 2012)

As outlined in section 1.1, most evidence points to the indoor environment as the myopia generating stimulus. One hypothesis singles out the high percentage of indoor time spent viewing near stimuli as the stimulus driving the progression of myopia. Therefore, it is critical for a myopia control lens design to ensure that both the vision quality and myopia control signal are maintained during near viewing. The myopia control contact lens design investigated in this thesis was specifically created to deliver approximately stable amounts of vision correction and myopic controlling signals across a range of pupil sizes. (Anstice and Phillips 2011)

A simple two zone design containing a single distance correction and a single zone with added plus power to create the myopia controlling myopic defocus signal have been used in animal studies (Liu and Wildsoet 2011, Liu and Wildsoet 2012) and human trials. (Walline, Greiner et al. 2013) Such 2-zone designs are unable to maintain a stable balance of vision correction and myopia control signals to the retina because, (Remón, Pérez-Merino et al. 2020) as the pupil dilates, the outer defocus zone will cover an increasing proportion of the pupil (Bradley, Nam et al. 2014, Charman 2014). Similarly, the proportions of vision correction and myopia control light within the retinal image will vary dramatically across the retina with such designs. (Hastings, Tiruveedhula et al. 2024) However, by employing a multi-zone design, the proportion of distance correction and myopia control signals can remain approximately balanced as pupil size increases. (Bradley, Nam et al. 2014, Charman 2014) The optical zone of the dual focus lens that is the topic of this research incorporated four alternating zones with a vision correction in a 3.35mm diameter center zone (CZ) surrounded by annular zones of interleaves added plus power and distance correction (Figure 1). A second annular distance correction zone surrounds the annular zone designed for myopia control, and finally a second outer annular myopia control zone (Figure 1). The zone geometries enable a delivery of a general dominance of the vision correction optic to ensure high quality vision, while also delivering a significant amount of myopia control signal for a wide range of pupil sizes

expected in children at the lower light levels present in the indoor environments, (Silbert, Matta et al. 2013) and to provide essentially single vision quality optics when children are not in the myopigenic indoor environments but in the high luminance outdoor environments. Where pupil diameters of young eyes can be <4mm. (Lazar, Degen et al. 2024) Best vision is generally achieved when focusing the central region of the pupil in an aberrated eye, and studies of eyes fit with either center near or center distance multifocal contact lenses observed that best distance vision and distance optical quality is achieved when the center of the lens contains the distance correcting optics. (Xu, Bradley et al. 2013, Hair, Steffensen et al. 2021) By assigning a relatively large region of the dual focus CL center for distance correction, the studied lens gave optical and visual priority to distance vision.

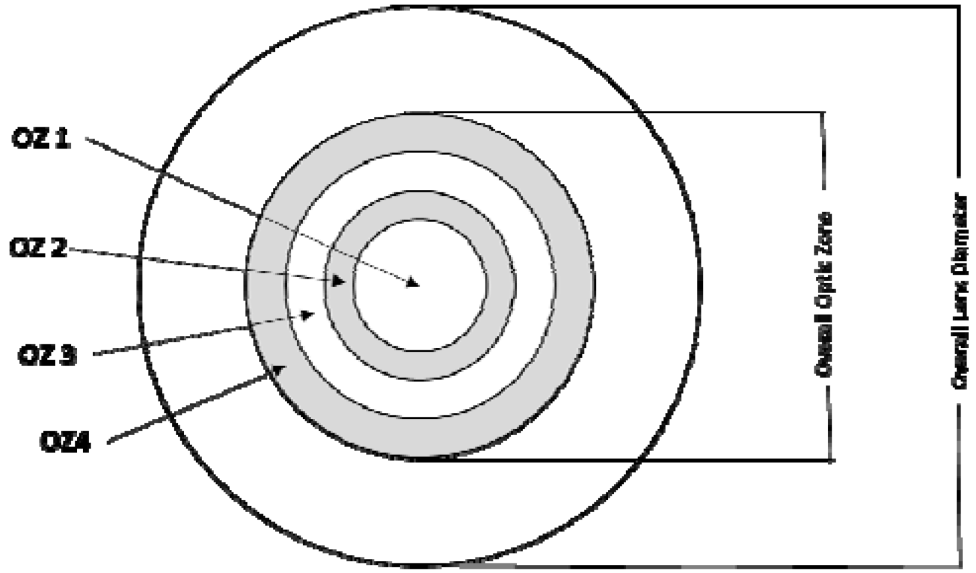


Figure 1: Optic zone arrangement of MiSight contact lens. Shaded areas indicate defocus zones.

This design approach results in a combination of refractive correction and myopia control optics for all pupil sizes greater than 3.35mm (Figure 2a). Because soft contact lenses center well on the cornea, they are generally decentered by on average 0.25mm relative to the pupil center and primary line of sight (Walther). Such small decentrations will ensure the dual focus distance correction center zone will remain within the pupil.(Walther, Meyer et al. 2024) More significantly, due to the axial separation of the contact lens on the corneal anterior surface and the eye's entrance pupil, a parallax effect will alter the proportion of distance correction and myopia control optics in the retinal image for off-axis targets, but again, a balance between distance correction and myopia control is maintained over a wide region of the central retina and pupil sizes (Figure 2b).

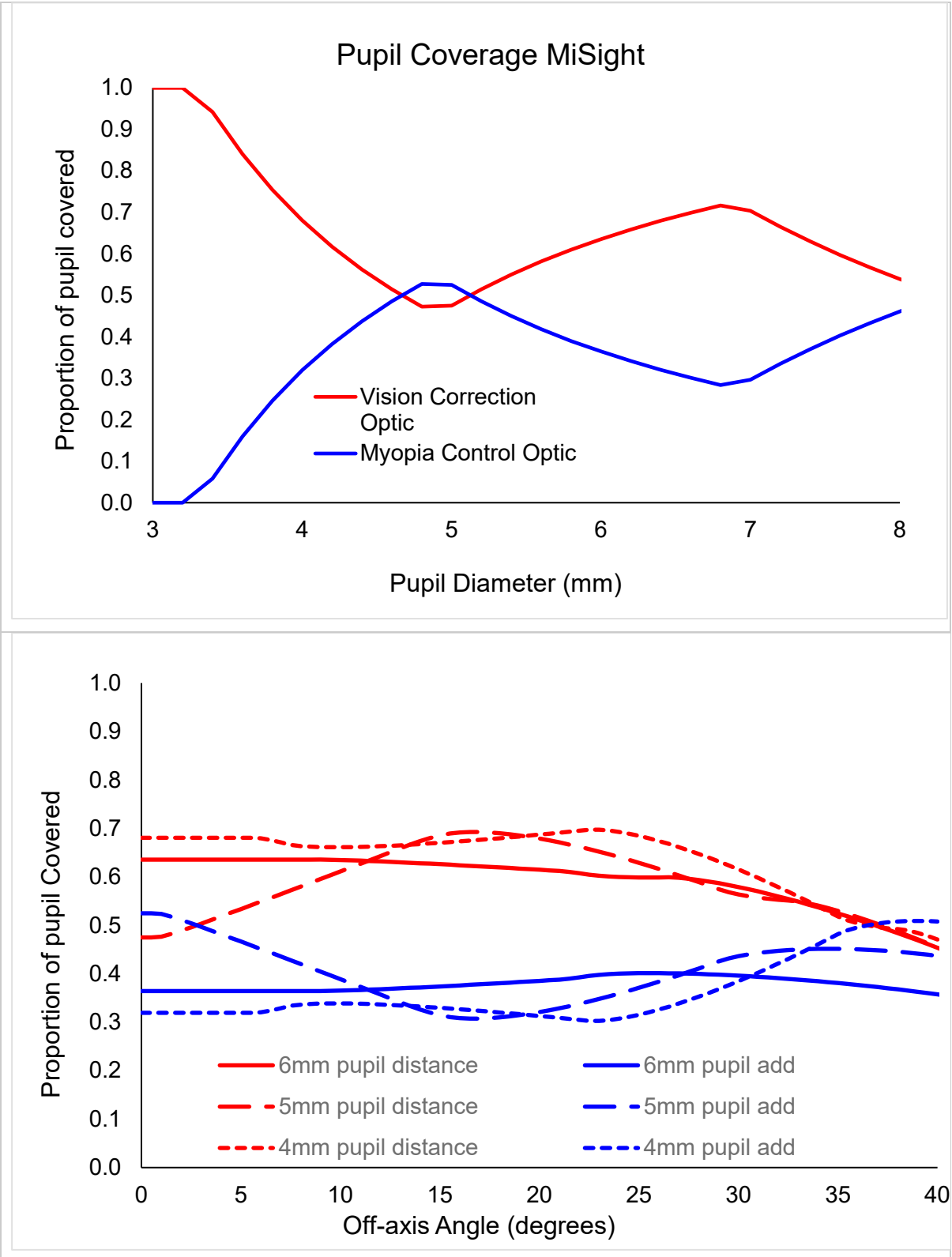


Figure 2 Proportion of pupil covered by the vision correction (red) and myopia control (blue) zones of the MiSight contact lens as a function of pupil diameter (top panel) and off-axis location of a light source (bottom panel) A parallax model was used to calculate the off-axis values assuming an axial separation of 3.5mm between the contact lens and the eye entrance pupil**.** The y-axis, "Proportion of pupil covered," represents the fractional area of the pupil occupied by each zone, calculated as the ratio of the zone's effective area to the total pupil area, reflecting the lens's optical contribution to vision correction and myopia control.

The pupil coverage results in Figure 2 highlight the achieved goals of this lens design: to provide a retinal image dominated by a refractive error-correcting distance vision optic, but including a significant proportion of myopically defocused light to act as a myopia control signal that is resilient to changes in pupil size and lens decentration, and delivers this myopia control signal across the central retinal area since there is evidence that the retinal location other than the fovea may contribute to eye growth regulation. (Smith 2011)

2.2. Choice of defocus power in dual focus lens design and power profile information

The treatment zones (Figure 1) were designed to incorporate approximately 2 dioptres of added plus (2 diopters of less minus) relative to the base or distance lens power (Figure 3, left panel). An early version of this dual focus design was studied by Anstice et al.(Anstice and Phillips 2011) The current design is modeled on that earlier design, including the choice of added plus 2 dioptres in the treatment zone. Small adjustments were made to zone diameter to adapt for the manufacturing platform used for this version of the lens design. Prior to the current investigation, Phillips et al examined the impact of adding +2D to a sphere correction for one eye only, the other eye having its typical distance correction lens. Eyes with the added plus 2D of power exhibited a consistent slowed myopia progression and axial elongation.(Phillips 2005)

The targeted power profile (Figure 3 left panel) and the full power map (Figure 3 right panel) of the studied lens reveal the concentric ring nature of the design and the stable powers within each zone. Unlike many optical power profiles designed for presbyopic correction, the distance power within MiSight is constant across the full radius of the zone. This deliberate feature was included to ensure high quality optics for the primary function of correcting refractive error and providing high quality vision for the patient. Many optical designs for correcting presbyopia, some of which have been employed off label for myopia control, (Walline, Greiner et al. 2013, Walline, Walker et al. 2020) may feature a radially varying “multifocal” power profiles across the lens providing increased depth of focus but possibly compromising distance vision quality. Multifocal designs with little area dedicated to distance vision correction will result in inferior distance vision image quality . (Chateau and Baude 1997) The juvenile myopic population targeted for this treatment have a full range of accommodation, (Anderson, Glasser et al. 2010) and as such have no need for a range of focal planes and its associated vision compromise and are expected to accommodate to near targets, using the distance correction optics of the dual focus lens for vision at all distances. Experimental studies of young eyes fit with multifocal and dual focus contact lenses confirm that with binocular viewing, accommodation is dominated by the distance correction optic (Altoaimi, Kollbaum et al. 2018) as expected given the dominant influence of binocular vergence on accommodative behavior. (Fincham and Walton 1957, Ramsdale and Charman 1988) Although the dual focus lens was designed to prioritize vision quality, image quality and vision were monitored during the trial (Chapter 4).

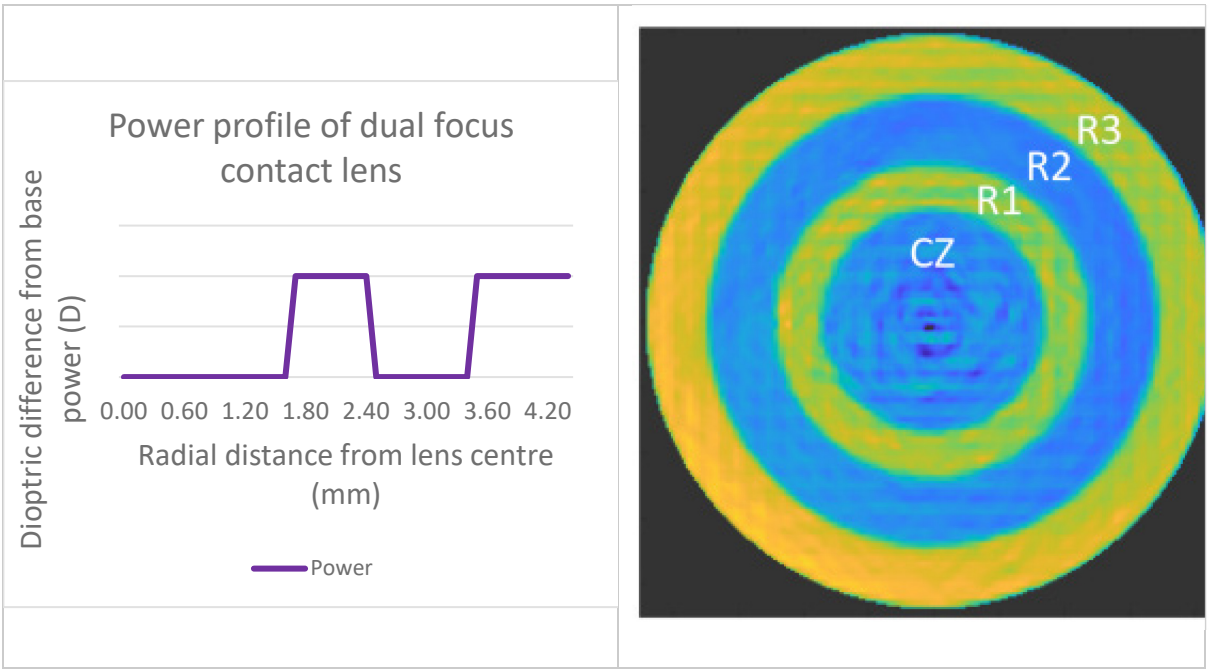


Figure 3: Power and zone geometry of the studied dual focus myopia control contact lens. The power profile (left panel) is the design ideal, whereas the power map (right) was obtained using a high-resolution single pass aberrometer (Optocraft) from a single contact lens. Distance correction zones (blue) and added myopia control zones (yellow) reveal the stable power in each zone, and the abrupt power shifts between zones.

CHAPTER 3: A THREE-YEAR CLINICAL TRIAL OF A DUAL FOCUS MYOPIA CONTROL LENS

3.1. STUDY DESIGN CONSIDERATIONS

The original dual focus design incorporating 2D of myopic defocus underwent feasibility testing in a contralateral eye cross over study over 20 months, where the efficacy of the design to slow myopia progression was assessed for each eye in successive 10 month treatment periods. (Anstice and Phillips 2011) Children in this study were slightly older (recruitment criteria: age - 11 to 14 years) than those monitored in many studies for myopia control. The results in that study confirmed the hypothesis of excellent visual acuity and normal accommodative response with this dual focus design. The dual focus intervention showed a statistically and clinically significant slowing in the progression in both periods. Spherical Equivalent Refraction (SER) was slowed by approximately 0.25D, whilst axial length elongation (AL) was slowed in each period by approximately 0.1mm. Each of these outcomes, translated to a myopia control efficacy measure of the amount of slowing expressed as a proportion of the untreated progression [((Control eye progression – Test eye progression) / Control eye growth) x 100%] of approximately 50%.

This study had a few limitations both from a scientific and translational perspective. Whilst having the advantage of each child acting as their own control for demographic and environmental factors influencing myopia progression, a contralateral eye study nonetheless poses challenges in interpretation of the findings. Although the study implemented measures to avoid right eye and left eye lens confusion, such as tinting the contact lens for the right eye, long-term contralateral studies can result in unintentional mixing of interventions between the right and left eyes. In a contralateral study, where a single vision correction is applied to the non-treated eye, there is a potential for better binocular accommodation than might occur with bilateral prescription of a dual focus myopia control lens.

A further limitation in extrapolation of those preliminary results was the potential confounder of prior treatment of the eyes that were untreated in part 2 of the study. Also, during part 2, these subjects were generally anisometropic due to different progression rates during part 1 of the study. (Anstice and Phillips 2011) The impact of anisometropia on eye growth regulation is poorly understood, but some evidence suggests anisometropia can influence eye growth.(Abrahamsson and Sjöstrand 1996) With concerns of carry-over effects potentially impacting Part 2 results, conclusions were largely limited to the results of Part 1, which in turn only illustrates an efficacy duration of 10 months. As mentioned in earlier sections, Juvenile onset myopia is likely to persist for greater than a decade of progression in some individuals, and therefore to establish the clinical value of this dual focus lens design, longer trials with bilateral treatment protocols were required.

The clinical trial of this novel myopia control contact lens was designed to answer the following scientific and clinical questions:

- Does the addition of 2D of added plus power in two annular zones in this dual focus CL generate a clinically and statistically significant treatment effect in juvenile myopic subjects when prescribed bilaterally?
- Can a treatment effect be sustained over multiple years? (at the start of this study in 2012, no randomized clinical trial had successfully shown treatment efficacy sustained over 2 years)
- Will the lens be effective at slowing myopia progression for a cohort of emerging young myopes (8-12 years)? (Myopia progression rates are generally higher in younger eyes, (Chua, Sabanayagam et al. 2016) the Anstice feasibility study enrolled children between ages 11 and 14). (Anstice and Phillips 2011)
- Will geographic location and/or subject ethnicity influence efficacy? (Myopia prevalence, progression and levels vary between countries and

ethnicities).(Rudnicka, Kapetanakis et al. 2016) The interaction between these features of the condition to myopia control results was unknown.
- Will treatment effect vary with age and gender? (Untreated younger myopic children and females have been shown to display faster progression). (Chua, Sabanayagam et al. 2016);(Donovan, Sankaridurg et al. 2012)
- What are the ocular health implications of all day, 6 days per week, and multiple years of contact lens wear in children?
- Will myopic children adapt to contact lens wear and accept this as their habitual vision correction and myopia control therapy? (If myopia control efficacy requires a consistent exposure to the treatment optic, successful treatment may require all day wear on most days). (Rah, Walline et al. 2010)
- Can significant myopia control be achieved without serious compromise of normal vision?

All of these factors were as yet unanswered and were considered critical to enable successful translation of a myopia control soft contact lens intervention into general clinical practice globally.

3.2. Study design and measures to eliminate bias.

The design of this trial progressed alongside discussions with regulatory agencies to address the requirements for obtaining regulatory approval and, crucially, a clear indication for use for slowing of myopia progression. This indication would provide eye care practitioners with explicit "on-label" prescribing guidance. At the time, the United States Food and Drug Administration (FDA) presented detailed requirements for achieving such an indication. Several years after the trial protocol was finalized, the FDA co-sponsored a workshop in collaboration with leading professional organizations representing optometry and ophthalmology in the U.S. The workshop aimed to establish a consensus on the design and conduct of clinical trials necessary for FDA approval and an appropriate indication for use, as formal guidance was not yet available. The resulting framework focused on providing "reasonable assurance of safety and effectiveness" for the device. The findings from this workshop were subsequently published in a peer-reviewed manuscript by Walline et al. (Walline, Robboy et al. 2018) The study protocol implemented for the MiSight clinical trial reflected opinions of the FDA as detailed during this workshop and resultant publication.

Multi-center trial and ethnicity – To provide evidence that the treatment results were broadly generalizable and not limited to a single geographic region, the study recruited participants from three continents: North America, Europe, and Asia. Each site was tasked with recruiting an equal number of participants, and a unique randomization schedule was provided to each location. This approach ensured an equal balance between treatment and control groups at each site. Myopia has been shown to onset earlier (Rudnicka, Kapetanakis et al. 2016) and progress more rapidly (Donovan, Sankaridurg et al. 2012) in Asian populations. Including an Asian site with equal randomization between treatment and control groups was a deliberate effort to achieve an appropriate balance of ethnic representation and ensure the results reflected diverse population outcomes.

Age – Similar to ethnicity, studies of myopia progression in Asian (Chua, Sabanayagam et al. 2016) and Western populations, (Jones-Jordan, Sinnott et al. 2021) show myopia progressing slower in older children regardless of when Myopia onsets. A meta-analysis (Brennan, Shamp et al. 2024) of 64 studies of axial growth in myopic eyes identified separate mathematical predictions for Asian and Non Asian populations. This analysis highlights a number of important considerations: (1) Asians progressed faster than non-Asian at every age (2) Each population displayed faster progression at younger ages, with progression slowing by 15% at each advancing year for both populations. A later meta-analysis suggested slowing of 10% per year for refractive error progression. (Smotherman, Brennan et al. 2023) Therefore,

without well balanced control and treatment cohorts, the associated factors of age and ethnicity will likely affect the mean progression and growth rates. The dual focus study design tried to limit the impact of cohort differences in these associated factors by stratifying randomization, requiring each site to recruit a balanced population by age groups of 8-10 and 11 - <13.

Choice of control intervention and masking – The potential for bias, whether conscious or unconscious, on the part of patients (or also parents, in this case) or investigators is well-documented. (Kotz and West 2022) Bias can arise from factors such as the collection of primary outcome measures or instructions that inadvertently influence behavior in either the test or control group. This risk becomes even more significant in long-term trials conducted over multiple years, as in this study.

In the MiSight trial, the control group would not receive active treatment, which increases the likelihood of bias due to a greater risk of loss to follow-up in untreated and potentially faster progressing eyes. (Kristman, Manno et al. 2004) While single-vision spectacle lenses are the most commonly used ophthalmic correction for children in this age range, their use as the control intervention posed significant challenges. Specifically, maintaining masking with a spectacle control group is virtually impossible. Additionally, disparities in wearing time between test and control groups can introduce bias, potentially skewing the observed treatment effects. Data from the ACHIEVE study (Walline, Jones et al. 2008) revealed that contact lens wearers had a significantly higher total wearing time for corrective lenses (Contact lenses and Spectacles: mean 97.5 hours/week) compared to Spectacle wearers ($p = 0.0006$). If both the treatment and control groups wear soft contact lenses, differences in wearing time are likely to be reduced or eliminated, enabling a more valid assessment of the treatment effect. Further, given the quality of life advantages experienced by young CL wearers over spectacles,(Walline, Jones et al. 2009, Rah, Walline et al. 2010) both the treated and control subjects share the lifestyle benefits of CLs which would balance retention motivations and increase the likelihood of matched environmental experiences between the two groups .

At the time of the study design, concerns were present that single vision contact lenses might induce greater myopia progression in progressing myopes, potentially exaggerating the observed myopia control effect. A study by Walline et al assessed this hypothesis in a large parallel group study. (Walline, Jones et al. 2008) The study found greater refractive progression in the contact lens wearing group, but the reported –0.22 D greater progression in the contact lens group was not statistically greater (95% CI: –0.46 to +0.02 D) than observed in the spectacle lens group. Additionally, axial length changes between the two groups were greater in the spectacle lens group and again not statistically significant (contact lenses: 0.59 ± 0.37 mm; spectacles: 0.63 ± 0.34 mm; $P = 0.37$).

Horner et al. (1999) randomized 175 adolescents (aged 11–14) to wear either reusable soft contact lenses or spectacles, focusing solely on refractive error. After three years, myopia progression was –1.07 ± 0.85 D in the contact lens group and –0.91 ± 0.80 D in the spectacle group, a difference that was not statistically significant. (Horner, Soni et al. 1999) Also, six-month myopia progression comparison between CL and SL wearers found less progression in the CL corrected eyes (–0.37 ± 0.29 D) compared to the spectacle group (–0.60 ± 0.29 D, $p < 0.001$), with a 44% smaller axial length increase (contact lenses: 0.14 ± 0.12 mm; spectacles: 0.25 ± 0.12 mm, $p < 0.001$). (Jara, Sankaridurg et al. 2010) An analysis of Asian children (ages 6–16) wearing single-vision spectacles ($n = 633$) or contact lenses ($n = 55$) found no significant difference in age-specific annual myopia progression (SER, $p = 0.38$) across prospective studies in China, Hong Kong, and Singapore. (Sankaridurg, Holden et al. 2014)

Given the benefits to reduce the risk of bias and the almost zero likelihood of single vision contact lens wear disrupting the myopia progression rates, the MiSight trial was designed with a single focus soft contact lens as the control intervention. To increase likelihood of effective

masking, the single vision soft contact lens was chosen as Proclear 1 day, CooperVision Inc. As a further enhancement to masking, the test and control contact lenses benefited from being fabricated from the same material, contained the same geometrical features and were produced with identical manufacturing processes. In fact, the only difference in the lens making process was the front contact lens surface mold to produce the optical features detailed in Chapter 2. The back surface and mold of the contact lens are identical in test and control products. These similarities enhance the likelihood of identical lens fit performance and wearer comfort for the two cohorts. Additionally, the distance correction optics in both the treatment and control lenses (power range for the study -1.00D to -6.00D) included controlled negative longitudinal spherical aberration level of -0.60D over a 6mm pupil diameter.

Masking was then further enhanced by strategies applied to the lens packaging. The lens blisters, which are produced in a strip of five were closely matched between test and control lenses with no distinguishing features between test and control lens, except for lot numbers essential for lens traceability (Figure 4).

Figure 4: Lens blister and lens carton for study lenses in the MiSight trial. Lens A = Proclear 1 day; Lens B = MiSight 1 day

Participant selection criteria - Age range at baseline (8-12 years) and spherical equivalent range (-0.75 - -4.00D) were chosen to be representative of the target patient population identified for this product and to limit variability associated with age and level of myopia. Minus 4.00D was chosen at the top end of inclusivity to allow subjects estimated progression to maintain within product availability (-6.00D) and outside of definition of high or “pathological”

myopia, throughout the study duration. (Flitcroft, He et al. 2019) Often seen in tandem with a refractive error criterion, some trials have adopted an additional inclusion criterion of evidence of prior progression. (Cheng, Woo et al. 2014, Pauné, Morales et al. 2015, Aller, Liu et al. 2016, Polling, Tan et al. 2020) Whilst this could provide some advantages in avoiding participants in either group whose myopia had stabilized, this trial elected not to apply this criterion, preferring to ensure generalizability to all myopes that might present in clinical practices. Astigmatism was limited to <1.00D, to limit vision compromise due to uncorrected astigmatism leading to lower wearing times or dropout because the dual focus lenses were not toric lenses. The study selection criteria also set a limit on anisometropia in the refractive error criterion and excluded any prior myopia control treatment, an approach consistent with most myopia control studies to date. (Wolffsohn, Kollbaum et al. 2019) Finally, the study also required all participants to have no prior experience with contact lens wear, this enabled some uniformity when assessing data related to adaptation, wear time and subjective experiences.

Study Treatment Wearing Time: Some myopia control studies have observed significant variability in wearing time and attributed this 'lack of compliance' to the resultant measures of efficacy, which didn't meet expectations for the intervention. (Lam, Tang et al. 2014, Sankaridurg, Bakaraju et al. 2019) In an effort to ensure compliance, subjects were asked to provide "Agreement to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the 3-year study" at informed consent stage. As well as "Agreement to inform the study investigator if this schedule is interrupted." Concerns of safety related this full-time wear requirement were mitigated by the study contact lenses being provided in daily disposable modality and close monitoring of the subjects' ocular heath throughout the study.

3.3. Publication: A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control.

CLINICAL TRIAL

A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control

Paul Chamberlain, BSc (Hons),[1]* Sofia C. Peixoto-de-Matos, MSc,[2] Nicola S. Logan, PhD,[3] Cheryl Ngo, MBBS, MMed,[4] Deborah Jones, BSc, FAAO,[5] and Graeme Young, PhD, FAAO[6]

SIGNIFICANCE: Results of this randomized, double-masked clinical trial demonstrate the effectiveness of the MiSight soft contact lens in slowing myopia progression over multiple years.

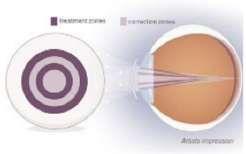
PURPOSE: The purpose of this study was to quantify the effectiveness of MiSight daily disposable soft contact lens in slowing the progression of juvenile-onset myopia.

METHODS: Myopic children (spherical equivalent refraction, −0.75 to −4.00 D; astigmatism, <1.00 D) aged 8 to 12 years with no prior contact lens experience were enrolled in a 3-year, double-masked, randomized clinical trial at four investigational sites in four countries. Subjects in each group were matched for age, sex, and ethnicity and were randomized to either a MiSight 1-day contact lens (test) or Proclear 1-day (control; omafilcon A) and worn on a daily disposable basis. Primary outcome measures were the change in cycloplegic spherical equivalent refraction and axial length.

RESULTS: Of the subjects enrolled, 75.5% (109/144) completed the clinical trial (53 test, 56 control). Unadjusted change in spherical equivalent refraction was −0.73 D (59%) less in the test group than in the control group (−0.51 ± 0.64 vs. −1.24 ± 0.61 D, $P < .001$). Mean change in axial length was 0.32 mm (52%) less in the test group than in the control group (0.30 ± 0.27 vs. 0.62 ± 0.30 mm, $P < .001$). Changes in spherical equivalent refraction and axial length were highly correlated ($r = -0.90$, $P < .001$). Over the course of the study, there were no cases of serious ocular adverse events reported. Four asymptomatic corneal infiltrative (one test, three control) events were observed at scheduled study visits.

CONCLUSIONS: Results of this clinical trial demonstrate the effectiveness of the MiSight daily disposable soft contact lens in slowing change in spherical equivalent refraction and axial length.

Optom Vis Sci 2019;96:556–567. doi:10.1097/OPX.0000000000001410



Author Affiliations:
[1]CooperVision Inc., Pleasanton, California
[2]Clinical and Experimental Optometry Research Lab, Centre of Physics, School of Sciences, University of Minho, Braga, Portugal
[3]Ophthalmic Research Group, School of Optometry, Aston University, Aston Triangle, Birmingham, United Kingdom
[4]Department of Ophthalmology, National University Hospital, Singapore
[5]Centre for Ocular Research and Education, School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada
[6]Visioncare Research Ltd., Farnham, Surrey, United Kingdom
*pchamberlain@coopervision.com

Myopia represents a growing public health issue, affecting 33% of adults in the United States[1] and markedly higher proportions in Asia.[2–4] Increasing myopia is associated with increased risk of retinal detachment,[5] glaucoma,[6] cataract,[7] and myopic retinopathy.[8] Higher levels of myopia are also associated with increased disability[9,10] and poorer refractive surgery outcomes.[11]

In the past decade, there has been increased research activity aimed at slowing the progression of myopia by optical methods, including overnight corneal reshaping contact lenses (orthokeratology)[12–14] and soft contact lenses incorporating multifocal or aspheric optics,[15–24] and these have shown promise to slow myopia progression.

Studies of the mechanisms that regulate refractive development in nonhuman primates show that hyperopic defocus can induce excessive eye growth and myopia and that myopic defocus can retard or reverse eye growth.[25] Further research has shown that eye growth can be manipulated when defocus, particularly myopic defocus, is presented simultaneously with an additional optical power. These simultaneous optics are typically used with concentric alternating powers in a zonal design within the lens optic and are commonly referred to as "dual-focus optics." Lenses with dual-focus optics have been used in a number of animal models, such as chickens, guinea pigs, marmosets, and rhesus monkeys, with the aim of retarding eye growth. All of these studies[26–32] have consistently shown that adding simultaneous myopic defocus to either hyperopic or plano correction resulted in reduced eye growth when compared with the control animals or fellow control eyes.

This principle of applying myopic defocus via a dual-focus optical design has been studied in clinical trials of human subjects. Anstice and Phillips[15] evaluated a dual-focus soft contact lens in children aged 11 to 14 years. This dual-focus design had a central zone containing the distance correction with concentric peripheral zones, alternating myopic defocus (additional positive power) with distance correction power. The intent of this optical design was to fully correct refractive error but simultaneously create myopic defocus in all directions of gaze. The central correction zone was

made sufficiently large for good visual acuity, but also to ensure that normal accommodation would be stimulated for near work. The zone diameters were designed to achieve constant presentation of myopic defocus to the retina. The dual-focus lens was compared in a contralateral study design with a single-vision soft contact lens. The mean 10-month change in spherical equivalent refraction in the eye wearing the dual-focus lens was significantly less than that in the contralateral eye wearing the single-vision lens (–0.44 vs. –0.69 D). The mean axial elongation was also significantly less with the dual-focus lenses (0.11 vs. 0.22 mm) than with the single-vision lenses.

This dual-focus optical design is the basis for the MiSight soft contact lens (CooperVision, Inc., Pleasanton, CA). Myopia progression was recently studied in 89 children aged 8 to 12 years in a 2-year parallel-group study comparing MiSight with standard single-vision spectacles.[23] In this study, the mean change in spherical equivalent refraction and the mean axial elongation were significantly less in the MiSight group than in the spectacle control group (–0.45 vs. –0.74 D, 0.28 vs. 0.44 mm).

The purpose of the current study is to report the results from a clinical trial of MiSight lenses with dual-focus optics compared with a single-vision contact lens of the same lens material and overall geometry. The clinical trial was designed to quantify the effectiveness of the MiSight lenses for slowing juvenile-onset myopia progression. The primary outcomes for effectiveness were change of cycloplegic spherical equivalent refractive error and axial length over the 3-year period. Additional end points included assessment of best-corrected visual acuity and subjective responses.

METHODS

Study Design

This study was a multicenter, parallel-group, double-masked, randomized clinical trial (ClinicalTrials.gov identifier: NCT01729208) of a daily wear, daily disposable myopia control soft contact lens compared with a standard daily disposable lens. The duration of the study was 3 years.

The study was performed at four investigational sites: University of Minho, Portugal; Aston University, United Kingdom; National University Hospital, Singapore; and the University of Waterloo, Canada. The study was conducted in conformance with the ethical principles in the Declaration of Helsinki, with the International Conference on Harmonization Good Clinical Practice guidelines and all applicable local regulations. The protocol, consent, and assent documents, along with all recruitment materials, were approved by each institution's institutional review board before commencing the study.

The test product, MiSight, and the control lenses, Proclear 1-day (CooperVision, Inc.), are both soft (hydrophilic) contact lenses composed of omafilcon A material. The study contact lenses were identical for both material and lens overall geometry and differed only in the optical design of the contact lens.

To ensure standardized measurements across sites, all sites were provided with the same protocol and trained before study initiation. Identical equipment calibration instructions were implemented for each site.

Subjects were recruited between November 2012 and April 2014. An assent document was explained to, read, and signed by each potential study subject before enrollment in the study. Similarly, a consent document was explained to, read, understood, and signed by a parent or legal guardian of the subject before enrollment.

All the inclusion and exclusion criteria are listed in Table 1. Children with spherical equivalent refractive error between –0.75 and –4.00 D inclusive with less than 1.00 D of astigmatism or anisometropia were eligible for the study. The study population was children aged 8 to <13 years at the baseline examination with targeted enrollment of a minimum of 50% of the study population in the 8- to 10-year age group.

At baseline, subjects were assessed for eligibility, which included ocular characteristics such as refraction, visual acuity, binocular status, and ocular health (Table 1). Subjective refraction was performed using a phoropter and projector chart at 6 m. Cycloplegic autorefraction and axial length measurements were performed as described in detail hereinafter.

Eligible subjects were sequentially randomized into either the MiSight or control group (1:1 ratio). The randomization procedure was stratified by clinical site and age group using a random permuted block design to achieve the 50% target of the younger-age group. The randomization log was created centrally by the contract research organization using a random number–generating computer program. Each clinical site was given a randomization log to assign the order in which subjects were dispensed the lens types. The randomization log was stored in the study documentation, so all investigators could access it, but the study product was coded (lens A and lens B) and the randomization log only had the lens codes listed on it. This code was also the only identifying feature on the study product. Participants and their parents were masked.

A lens-fitting procedure was performed where the contact lens power for the subject was finalized, and acceptable lens fitting was confirmed. The subject was dispensed once he/she had successfully completed training for insertion and removal of the contact lenses. Both the MiSight and control lenses were used following a daily wear, daily disposable modality. Progress was monitored at follow-up visits at 1 week, 1 month, and 6, 18, 24, 30, and 36 months.

Cycloplegic spherical equivalent refraction and axial length were assessed at baseline and at the annual follow-up visits. Cycloplegia was produced by first instilling one drop of anesthetic, either 0.5% proparacaine or 0.4% benoxinate, in each eye. One minute later, one drop of 1% tropicamide was instilled in each eye, followed by a second drop 5 minutes later. The examiner waited at least 25 minutes before conducting further assessments.

Cycloplegic refraction was measured using the Grand Seiko Binocular Auto-refractor/Keratometer WR-5100K or WAM-5500 (Grand Seiko Co., Hiroshima, Japan). Subjects were instructed to view a 4-m distance target one line larger than their best acuity; subsequently, 10 measurements were taken per eye and later averaged. Axial length was measured using the IOLMaster (Carl Zeiss Meditec, Dublin, California), with the subject fully cyclopleged. Subjects were instructed to view the internal fixation target, and 10 measurements were taken of each eye.

Visual acuity was assessed using ETDRS Revised 2000 Series Charts (Precision Vision, Woodstock, IL) using by-letter scoring (0.02 logMAR). The charts were standardized to a luminance of 85 cd/m^2. With the subject wearing the appropriate distance vision correction and left eye covered, the subject began at 20/50 line, reading the first letter on each successive line until he/she made an error. When the subject made an error, he/she was asked to read progressively larger lines until the subject was able to correctly

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Be between 8 and 12 y of age inclusive at baseline examination	Current or prior contact lens wear
The participant has been given a clear explanation, then read, understood, and signed the informed assent form.	Subject is currently or within 30 d before this study has been an active participant in another clinical study
The participant has been given a clear explanation, then read, understood, and signed the informed assent form.	Parent/guardian or close relative is a member of the office staff, including the investigator(s)
The parent or legal guardian has been given a clear explanation, then read, understood, and signed the informed consent form.	Current or prior use of bifocals, progressive addition lenses, atropine, pirenzepine, or any other myopia control treatment
Willingness to adhere to protocol, agreement to maintain the visit schedule	Birth earlier than 30 wk or <1500 g (3.3 lb) at birth
Along with their parent or guardian, agree to maintain the visit schedule and be able to keep all appointments as specified in the study protocol for the duration of the study	Regular use of ocular medications, artificial tears, or wetting agents
Acceptance of either the control or test lens as assigned by randomization	Current use of systemic medications, which may affect contact lens wear, tear film production, pupil size, accommodation, or refractive state
Agreement to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the 3-y study. Agreement to inform the study investigator if this schedule is interrupted	A known allergy to fluorescein, benoxinate, proparacaine, or tropicamide
Possess wearable and visually functional eyeglasses	A history of corneal hypoesthesia (reduced corneal sensitivity), corneal ulcer, corneal infiltrates, ocular viral or fungal infections, or other recurrent ocular infections
Be in good general health, based on his/her and parent's/guardian's knowledge	Strabismus by cover test at distance or near wearing distance correction
Best-corrected visual acuity by manifest refraction of +0.10 logMAR (20/25) or better in each eye	History of ocular or systemic diseases, including those that could influence refractive development
Meet the following refractive criteria determined by cycloplegic autorefraction at baseline: (*a*) Spherical equivalent refractive error: between −0.75 and −4.00 D inclusive (*b*) Astigmatism: ≤−0.75 D (*c*) Anisometropia: <1.00 D	Keratoconus or an irregular cornea
	Contraindications for contact lens wear including giant papillary conjunctivitis of grade 2 or worse and allergic or seasonal conjunctivitis
	Subject seems to exhibit poor personal hygiene (that in the investigator's opinion might prevent safe contact lens wear) or the investigator for any reason considers that it is not in the best interest of the subject to participate in the study

identify all five letters on a line. The subject continued reading until three or more letters were missed on a given line. Visual acuity was recorded in logMAR to the nearest letter, including the final read line. Near visual acuity was measured in logMAR notation with Near Point Flip Charts (Precision Vision) held at 40 cm. The same protocol for measuring distance vision was used to assess near vision under the same lighting conditions. Refractive status was assessed at each visit before cycloplegia. A change in lens power was provided at any study visit when subjective overrefraction was equal or greater than 0.50 D or a clinically meaningful improvement in visual acuity could be achieved (greater than ½ line). Lens fit and ocular health were also assessed at these visits.

Subjective feedback was obtained from both the participants and the parents via questionnaires at each follow-up visit. Questionnaires targeted information for lens handling along with assessments of comfort, vision, and overall satisfaction. Each question offered five Likert-type responses. The subjects were given ample time and asked to complete the questionnaire by themselves. A member of the site staff was available to answer any queries and to help the subject understand the question but was instructed not to help the subject with the answer.

For the purposes of demonstrating the general acceptance of the contact lenses in this trial population, this publication will present findings only for lens handling and overall satisfaction from the extensive questionnaire. Subjects were invited to rate their contact lens handling experience to choose from the following: really easy, kind of easy, neither easy nor hard, kind of hard, or really hard. For the overall satisfaction rating for wearing both their spectacles and contact lenses, the following choices were given to the subjects: I like them the best, I kind of like them, neither like them nor do not like them, I do not like them, and I cannot stand them.

Wearing time was collected by asking participants their typical lens insertion and removal times on a typical weekday and weekend and how many days in a week the lenses were typically worn. The wear time was calculated from these responses for each participant.

The primary outcomes for safety were assessed using slit-lamp biomicroscopy findings and ocular adverse event rates between

the MiSight and control groups. Adverse events were classified and reported according to a pre-determined list detailed in the study protocol. Slit-lamp signs were graded using a 0- to 4-point scale developed from the guidance illustrated in the regulatory standard ISO11980, with 0 representing none or absent findings and 4 representing severe. Unique supplementary descriptions were added to this scale for specific tissue grading.

Sample Size Estimation

The target effect size for sample size calculation was specified as "0.25 D per year (i.e., 0.75 D for 3 years)." This therefore produced two aims for the primary effectiveness end point; the first was to detect 0.25 D between groups for each year of the study. Using 0.25 D per year as a target and assuming a standard deviation of 0.50 D, it was estimated that 87 subjects per group would be needed (two-sample *t* test with equal variance, $\alpha = 0.05$, power = 90%). The protocol anticipated an enrollment target of 150 eligible subjects per group to account for attrition (14%, or 42 subjects per year) over the 3-year period.

However, because of a longer-than-expected recruitment period, it was evident that the number of subjects enrolled would be smaller than this target. As a consequence, the sample size requirements for the second aim, which was to detect a 0.75-D difference between the groups for 3 years, were applied. Assuming a standard deviation of 0.50 D, 22 subjects (11 per group) would have been needed (two-sample *t* test, $\alpha = .05$, power = 90%) to complete the study. As such, the final sample size of 144 eligible subjects was more than adequate to detect the primary effectiveness end point.

Statistical Methods

Baseline data for the MiSight and control groups were evaluated by the two-sample *t* test (continuous data), Mann-Whitney *U* test (categorical data), or Fisher exact test (nominal data). Imbalances of potentially confounding variables that were identified between the two groups were addressed by including them as covariates in the final analysis. All inferences were carried out with the type I error rate controlled at 5%.

Data were pooled from all sites based on three factors: (1) common protocol, (2) common data collection procedures, and (3) closely monitored protocol compliance. As specified in the protocol, an analysis of the interaction of lens type by site was performed and found not significant ($P > .10$) for the primary outcome variables.

The primary outcome measures for effectiveness were checked for normality and first compared between treatment groups using a *t* test. These primary outcomes were also compared using linear mixed models. Comparisons between the MiSight and control lenses were carried out using two-sided confidence interval constructed least-square mean differences at each follow-up visit. The model included treatment (lens type), visit, site, and the interactions: visit by treatment and site by treatment as fixed effects; age, sex, weekday wearing time, weekend wearing time, and baseline value as fixed covariates; and subject (nested in site) and eye as random effects. The inclusion of eye as a random effect accounts for any correlation between eyes. The analyses included all evaluable subjects who did not have a protocol deviation that rendered data unsuitable for inclusion. If a subject missed a primary outcome visit, no data were included for that visit, but all other visits with evaluable data for that subject were included. Data from discontinued subjects were included up to the point of their discontinuation. A statistical difference was concluded if the 95% confidence limit of the mean difference was greater than zero (test minus control). The questionnaire responses were compared with linear mixed models. The model included treatment (lens type), visit, site, and the interactions.

The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Data

Table 2 summarizes the demographics for all enrolled subjects. There were no statistically significant differences between the MiSight and control groups with respect to the critical demographic factors that have been associated with myopia progression. At baseline, the mean cycloplegic spherical equivalent refractive errors were –2.02 ± 0.77 D for the MiSight lens group and –2.19 ± 0.81 D for the control lens group. Axial length was also similar between the groups: 24.42 ± 0.70 and 24.46 ± 0.66 mm for the MiSight and control lens groups, respectively.

Subject Accountability

Fig. 1 shows the flow of participants through the clinical trial from recruitment to study completion and analysis. Of the 187 subjects who were screened, 144 were eligible and randomized. This number comprised 21 subjects in Portugal, 28 in the United Kingdom, 31 in Singapore, and 64 in Canada. The main reasons for ineligibility were spherical refractive error (15), cylinder (7), and anisometropia (5). Of those allocated treatment, six had unacceptable lens fits (three MiSight and three control), and two had challenges with lens insertion and removal, whereas one control subject elected to withdraw from the study during the first week.

TABLE 2. Subject demographics at baseline

Variable	Control (n = 74)	MiSight (n = 70)	*P*
Age (y)	10.1 ± 1.4	10.1 ± 1.3	.83
Range	8–12	8–12	
<10	42 (57%)	40 (57%)	
10–12	32 (43%)	30 (43%)	
Male	37 (50%)	38 (54%)	.62
Female	37 (50%)	32 (46%)	
White (European)	40 (54%)	39 (56%)	.79
East Asian	18 (24%)	16 (23%)	
West Asian	7 (9%)	5 (7%)	
Other	4 (5%)	2 (3%)	
Mixed	5 (7%)	8 (11%)	
	(n = 148 eyes)	(n = 140 eyes)	
Cycloplegic spherical equivalent (D)	–2.19 ± 0.81	–2.02 ± 0.77	.08
Range	–0.83 to –4.00	–0.77 to –3.77	
Cylinder (D)	–0.40 ± 0.21	–0.40 ± 0.21	.82
Range	0.00 to –0.75	0.00 to –0.75	
Axial length (mm)	24.46 ± 0.70	24.42 ± 0.66	.90
Range	23.0 to 27.0	22.7 to 26.0	

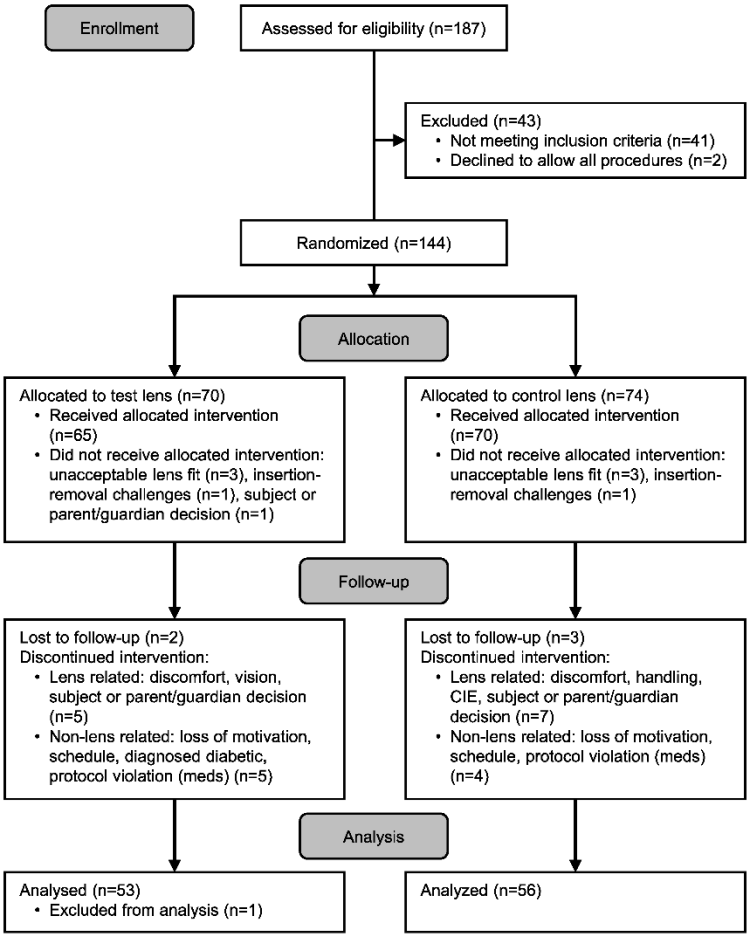


FIGURE 1. Flowchart to indicate the disposition of subjects from screening to study completion.

Thus, 135 subjects were dispensed the allocated intervention, ranging between 21 and 60 subjects per site.

One hundred nine subjects completed the 3-year clinical trial (53 MiSight and 56 control). One subject in the MiSight group was excluded from the 36-month analysis because the subject began a course of growth hormone treatment during the last 6 months of the study. The total retention rate for the study was 75.5%.

Compliance to the protocol-specified wearing time was high. The mean wearing times reported for weekdays at the 36-month visit were 13.3 ± 1.5 hours per day for the control group and 13.7 ± 1.5 for the MiSight group, and this difference was not significant. The mean wearing times reported for weekends were slightly lower but were 12.4 ± 0.9 and 12.1 ± 1.2 hours per day for the control and MiSight groups, respectively. The linear mixed model showed no differences between lens types for wear time at weekdays or weekends ($P > .05$). Subjects also reported the number of days per week that lenses were worn. The mean reported wearing times were at least 6.5 days per week for both lens groups. None of the above measures were significantly different between the groups.

Refractive Error Progression

The MiSight group exhibited less progression in cycloplegic spherical equivalent refraction than did the control group at each of the annual follow-up visits (Fig. 2, Table 3). In comparison with the control group, the changes in cycloplegic spherical equivalent refraction were on average 0.40 D less (–0.58 vs. –0.18 D) with MiSight at 12 months, 0.54 D less at 24 months,

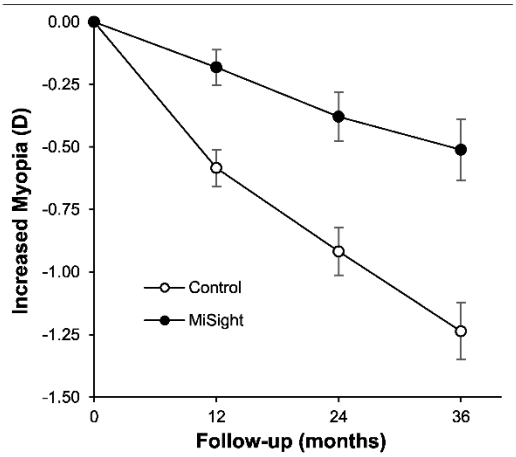


FIGURE 2. Mean unadjusted changes in spherical equivalent refractive error (D) for the test (MiSight) and control (Proclear 1-day) study groups. The filled and open symbols represent the MiSight and control groups, respectively, for the 36-month study period. The error bars denote the 95% CI of the mean changes. The mean unadjusted differences were 0.40 D less with MiSight at 12 months, 0.54 D less at 24 months, and 0.73 D less at 36 months. CI = confidence interval.

and 0.73 D less at 36 months. These differences were statistically significant at each time point (Student *t* test, $P < .0001$), representing myopia control effects of 69%, 59%, and 59%, respectively.

After adjusting for factors detailed in Statistical Methods, the least-square estimated mean progression was calculated. The estimated mean progression and differences are shown in Table 4. The adjusted differences in progression rate remained statistically significant at all follow-up visits.

Fig. 3 shows the distribution of individual subject's change in spherical equivalent refraction after 36 months. Among the MiSight lens–wearing eyes, 41% showed no clinically meaningful change in spherical equivalent refraction (defined as –0.25 D or less change) in comparison to 4% of the eyes in the control lens group. Conversely, 62% of the control lens–wearing eyes had progressed by more than –1.00 D compared with 18% of the MiSight eyes.

Axial Elongation

The MiSight group exhibited less axial length growth than did the control group at each of the annual follow-up visits. At 12 months, the change in axial length was 0.24 mm in the control group versus 0.09 mm in the MiSight group, representing on average a 0.15-mm less growth in the MiSight lens group. At 24 and 36 months, the change in axial length growth was 0.24 and 0.32 mm less in the MiSight lens group, respectively (Fig. 4, Table 3). These differences were statistically significant at each time point, representing myopia control effects of 63%, 53%, and 52%, respectively.

After adjusting for factors detailed in Statistical Methods, the least-square estimated mean change in axial length was calculated. The estimated mean change and differences between groups are shown in Table 4. The differences in axial length were statistically significant at all follow-up visits.

TABLE 3. Myopia progression for spherical equivalent and axial length

Visit	Study group	n (Eyes)	Spherical equivalent (D ± SD)	Change (D)	95% CI
Baseline	Control	148	–2.19 ± 0.81		
	MiSight	140	–2.02 ± 0.77		
12 mo	Control	120	–2.80 ± 1.01	–0.58 ± 0.41	–0.51 to –0.66
	MiSight	116	–2.17 ± 0.85	–0.18 ± 0.39	
24 mo	Control	120	–3.13 ± 1.08	–0.92 ± 0.53	–0.82 to –1.01
	MiSight	110	–2.33 ± 0.92	–0.38 ± 0.52	
36 mo	Control	112	–3.45 ± 1.14	–1.24 ± 0.61	–1.12 to –1.35
	MiSight	104	–2.52 ± 0.98	–0.51 ± 0.64	
			Axial length (mm)	**Change (mm)**	**95% CI**
Baseline	Control	148	24.42 ± 0.66		
	MiSight	140	24.46 ± 0.70		
12 mo	Control	120	24.68 ± 0.66	0.24 ± 0.15	0.21 to 0.27
	MiSight	116	24.52 ± 0.69	0.09 ± 0.13	
24 mo	Control	120	24.88 ± 0.70	0.45 ± 0.23	0.41 to 0.50
	MiSight	110	24.60 ± 0.64	0.21 ± 0.22	
36 mo	Control	112	25.07 ± 0.74	0.62 ± 0.30	0.57 to 0.68
	MiSight	104	24.76 ± 0.66	0.30 ± 0.27	

CI = confidence interval.

TABLE 4. Least-square mean estimates for spherical equivalent and axial length progression

Visit	Study group	Spherical equivalent change (D ± SD)	Difference (D ± SD)	95% Confidence interval	*P*
12 mo	Control	−0.64 ± 0.07	0.38 ± 0.09	0.21 to 0.55	<.0001
	MiSight	−0.27 ± 0.07			
24 mo	Control	−0.99 ± 0.07	0.52 ± 0.09	0.35 to 0.69	<.0001
	MiSight	−0.47 ± 0.07			
36 mo	Control	−1.31 ± 0.08	0.67 ± 0.09	0.49 to 0.84	<.0001
	MiSight	−0.65 ± 0.07			
		Axial length change (mm)	**Difference (mm)**	**95% Confidence interval**	***P***
12 mo	Control	0.23 ± 0.03	−0.13 ± 0.04	−0.21 to −0.05	<.002
	MiSight	0.10 ± 0.03			
24 mo	Control	0.45 ± 0.03	−0.22 ± 0.04	−0.30 to −0.14	<.0001
	MiSight	0.23 ± 0.03			
36 mo	Control	0.62 ± 0.03	−0.28 ± 0.04	−0.36 to 0.20	<.0001
	MiSight	0.34 ± 0.03			

Factors Impacting Progression

Statistically significant factors affecting refractive error progression and axial length elongation included lens type, investigative site, study visit, age, and sex (Table 5). Ethnicity and baseline myopia (refractive error or axial length) were not significant. There was a significant interaction of lens type and visit for refractive error progression and axial elongation, suggesting that the rate of change of the two lens types is different over the years. There was no significant interaction between lens type and site, suggesting that the myopia progression for both lens types was independent of investigative sites. The interaction of lens type with age, sex, or baseline myopia was not significant and was removed from the model. The absence of significant interactions of lens type with age, sex, baseline myopia, or investigative site demonstrates that the myopia control effect is independent of these factors in this study population.

Correlation between Changes in Axial Length and Refractive Error

There is a strong relationship between increasing myopia with increasing axial length. With the MiSight and control combined

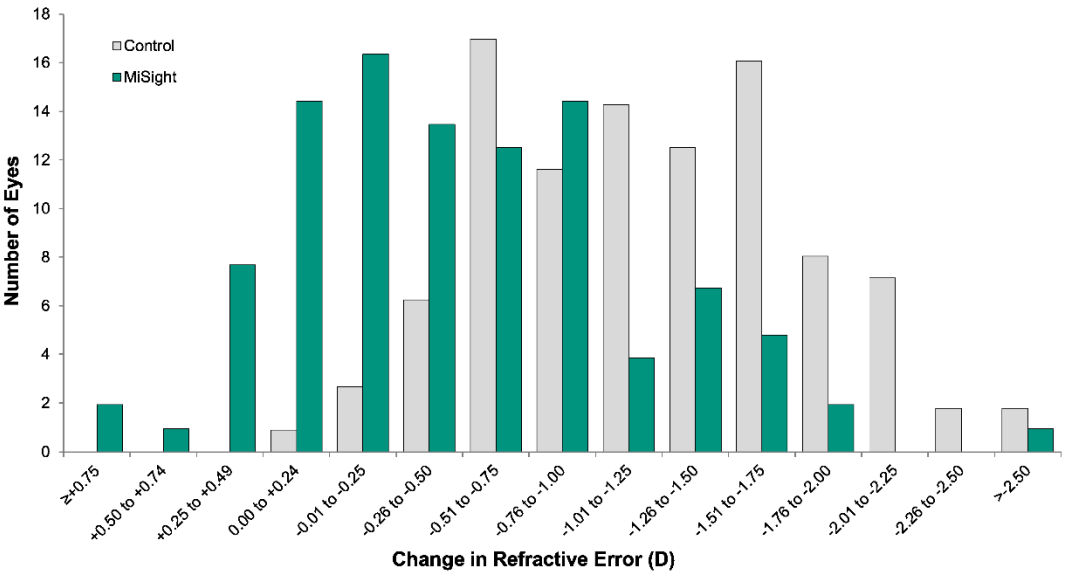


FIGURE 3. Frequency distribution of change in refractive error from baseline to 36 months. The filled and open bars represent the MiSight and control groups, respectively.

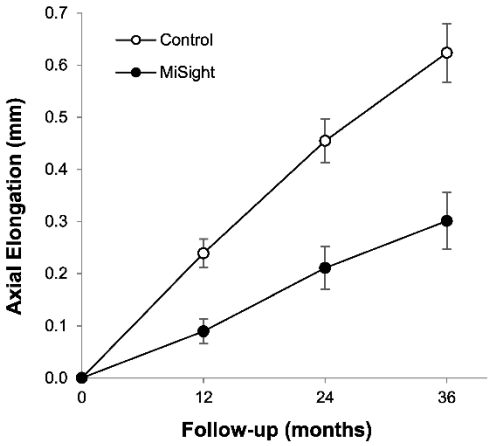


FIGURE 4. Mean unadjusted changes in axial length (in millimeters) for the test (MiSight) and control (Proclear 1-day) study groups. The filled and open symbols represent the MiSight and control groups, respectively, for the 36-month study period. The error bars denote the 95% CI of the mean changes. The mean unadjusted differences were 0.15 mm less with MiSight at 12 months, 0.24 mm less at 24 months, and 0.32 mm less at 36 months. CI = confidence interval.

data, there were statistically significant correlations at each of the follow-up visits ($P < .0001$). These correlations became stronger as the study progressed. At 12 months, the correlation coefficient (R) was –0.77; at 24 months, the R value was –0.86; and at 36 months, the R value was –0.90.

The correlations were also statistically significant at each follow-up visit when considered separately for the MiSight and control groups. At 36 months, the correlation coefficients were –0.89 ($P < .0001$) for the MiSight group and –0.85 ($P < .0001$) for the control group.

The slope for all subjects at 36 months was –0.42 (95% confidence interval, –0.45 to –0.39), showing that a 0.1-mm change in axial length corresponded to 0.24-D change in myopia in this study population. The slope did not vary significantly between treatment groups or among sites.

Contact Lens Visual Acuity

At the dispensing visit, mean distance visual acuity with contact lenses was within one letter for the MiSight lenses and control lenses (–0.03 ± 0.06 vs. –0.05 ± 0.07 logMAR). Mean visual acuity with contact lenses varied slightly at follow-up visits, possibly due to refractive error changes that occurred since the last visit, but did not differ by more than two letters at any visit. With spherical overrefraction, best-corrected visual acuity with contact lenses remained similar for the two lens types and within one letter at each visit. Near visual acuity remained within one letter for the MiSight and control lenses at each visit. The data for visual acuity are shown in Table 6.

Subjective Responses

Responses to the question "How easy is it to put the lenses on your eye?" were obtained. At the 1-month visit, a large proportion of children (>80%) in each group described insertion of lenses as "kind of easy" or "really easy" (top 2 box responses). Over the remainder of the study period, more than 90% of subjects rated within the top 2 box category. There was no difference between study groups in the response to this question ($P = .64$). With respect to lens removal, the responses to "How easy is it to take the lenses out of your eye?" remained in the top 2 boxes for more than 90% of the subjects throughout all visits of the study; again, there was no difference between study groups for this response ($P = .99$).

A positive response to the general experience of wearing contact lenses was also observed. For the question "How much do you like wearing your contact lenses?" an average of 97% of children chose one of the top 2 responses across all visits of the study. There was no difference between study groups in the response ($P = 1.00$). This was compared with a less positive response for spectacles, with an average of 57% choosing one of the top 2 responses to the question "How much do you like wearing your spectacles?" across all visits. The difference between groups approached statistical significance ($P = .05$). In general, this was due to higher variation in the response across the groups, throughout the study period.

TABLE 5. Tests of fixed effects for primary variables

	Refractive error			Axial length		
Model term	*df*	*F*	*P*	*df*	*F*	*P*
Lens type	1, 106	44.31	<.0001	1, 106	33.29	<.0001
Site	3, 104	13.26	<.0001	3, 106	4.90	.003
Visit	2, 209	119.89	<.0001	2, 209	245.13	<.0001
Age	1, 103	7.78	.006	1, 108	13.75	.0003
Sex	1, 103	9.20	.006	1, 122	4.43	.04
Ethnicity	4, 104	0.59	.67	4, 106	0.11	.98
Baseline spherical equivalent/axial length	1, 361	2.22	.14	1, 364	0.26	.61
Lens type × site	3, 105	1.08	.36	3, 107	1.70	.17
Lens type × visit	2, 209	9.03	.0002	2, 209	14.89	<.0001
Site × visit	6, 209	2.21	.05	6, 209	5.31	<.0001
Lens type × site × visit	6, 209	1.14	.34	6, 209	0.81	.56

TABLE 6. BCVA with contact lenses

	n (eyes)	Presenting contact lens VA	BCVA with spherical overrefraction	Presenting contact lens near VA
Control				
Dispensing	148	−0.05 ± 0.07	−0.05 ± 0.07	−0.07 ± 0.11
12 mo	120	+0.01 ± 0.13	−0.07 ± 0.08	−0.11 ± 0.11
24 mo	120	+0.00 ± 0.13	−0.07 ± 0.08	−0.11 ± 0.09
36 mo	112	+0.00 ± 0.10	−0.05 ± 0.07	−0.10 ± 0.08
MiSight				
Dispensing	140	−0.03 ± 0.06	−0.03 ± 0.06	−0.05 ± 0.10
12 mo	116	−0.04 ± 0.09	−0.07 ± 0.06	−0.09 ± 0.10
24 mo	110	−0.04 ± 0.10	−0.07 ± 0.08	−0.11 ± 0.09
36 mo	104	−0.01 ± 0.11	−0.05 ± 0.07	−0.09 ± 0.09

All values are in logMAR (mean ± SD). BCVA = best-corrected visual acuity; VA = visual acuity.

Safety Evaluation

There were no serious (events that are vision-threatening and result in permanent impairment of a body function or permanent damage to a body structure) or significant (events that usually are symptomatic but are non–vision-threatening and result in temporary impairment of a body function or temporary damage to a body structure) ocular adverse events reported in the 3-year study. There were 18 events (11 subjects) in subjects wearing the MiSight lens and 12 (10 subjects) with the control lens. Seven events (six subjects) with the test lens and seven events (five subjects) with the control lens were considered lens related. Four of these were asymptomatic corneal infiltrative events, one in the MiSight lens and three in the control lens group. The remainder of these events included foreign body, bilateral allergic reaction, unilateral mild pannus (requiring temporary discontinuation), superficial punctate corneal staining, a unilateral subconjunctival hemorrhage, and a case of irritation with the lens located under the eyelid. There were no reports of loss of best-corrected visual acuity.

There was only one instance of a slit-lamp finding of grade 3 or more. Grade 3 palpebral roughness was recorded in a MiSight lens–wearing eye at the 1-month visit. This was attributed to a

TABLE 7. Summary of previous studies of soft contact lenses on myopia progression

Authors	Duration (mo)	Analyzed test/ control	Discontinued (%)	Study design	Treatment lens	Control lens	Age (y)	Entry Rx range (D)	Treatment effect for axial length: Axial length difference (mm)	Treatment effect for axial length: Myopia control (%)
Anstice and Phillips[15]	10	35/35*	13	Randomized paired eye, crossover	Dual focus	Soft lenses	11–14	−1.25 to −4.50	0.11	49
Sankaridurg et al.[16]	12	43/39	18	Prospective	Progressive periphery	Spectacles	7–14	−0.75 to −3.50	0.15	38
Fujikado et al.[18]	12	11/13	0	Randomized masked, crossover	Menicon low-addition (Nagoya, Japan)	Soft lenses	10–16	−0.75 to −3.50	0.05	25
Aller et al.[21]	12	39/40	9	Randomized, masked	Acuvue Bifocal (Vistakon, a division of Johnson & Johnson Vision Care, Jacksonville, FL)	Soft lenses	8–18	−0.50 to −6.00	0.19	79
Cheng et al.[22]	12	53/59	16	Randomized, masked	Positive spherical aberration	Soft lenses	8–11	−0.75 to −4.00	0.14	39
Walline et al.[17]	24	27/27	33	Historical control	Proclear multifocal	Soft lenses	8–11	−1.00 to −6.00	0.12	29
Allen et al.[24]	24	45/50	33	Randomized masked	Aberration controlled monofocal	Soft lenses	14–22	−0.75 to −10.00	−0.01	−0.1
Lam et al.[19]	24	65/63	42	Randomized, masked	Custom concentric bifocal	Soft lenses	8–13	−1.00 to −5.00	0.12	32
Paune et al.[20]	24	19/21	44	Prospective	Radial refractive gradient	Spectacles	9–16	−0.75 to −7.00	0.14	27
Ruiz-Pomeda et al.[23]	24	41/33	7	Randomized, masked	MiSight	Spectacles	8–12	−0.75 to −4.00	0.17	36
Present study	36	52/56	19	Randomized, masked	MiSight	Soft lenses	8–12	−0.75 to −4.00	0.32	52

Rx = refraction.

foreign body and was not noted at subsequent follow-up visits. Palpebral roughness was graded from 0 to 4 as follows: 0 (none), uniform satin appearance of the conjunctiva; 1 (trace), slight conjunctival injection without texture; 2 (mild), mild or scattered papillae/follicles less than 1 mm in diameter; 3 (moderate), (*a*) significant papillae/follicles less than 1 mm in diameter and/or marked conjunctival injection and (*b*) staining of the top of one papilla; and 4 (severe), (*a*) localized or generalized papillae/follicles 1 mm or more in diameter and (*b*) staining of the top of more than one papilla.

DISCUSSION

The findings of this 3-year randomized clinical trial demonstrate that myopia progression is significantly slowed by the MiSight soft contact lens. MiSight lenses showed less unadjusted refractive error change by 0.40 D at 12 months, 0.54 D at 24 months, and 0.73 D at 36 months compared with the single-vision control contact lens. This was closely mirrored by a reduction in axial elongation of 0.32 mm at 36 months in the MiSight group. The strong correlation between axial elongation and refractive error progression demonstrates that the lenses slow myopia progression by reducing the rate of axial growth.

Table 7 presents a summary of other clinical trials that utilized soft contact lenses for myopia control, arranged by trial duration. This current clinical trial presents 3-year results, whereas all of those summarized in Table 7 are 1- or 2-year studies. The reduction in myopia progression reported here approaches the greatest observed effect size from previously published studies. However, the absence of studies of similar duration makes comparison of effect size difficult.

Ruiz-Pomeda et al.[23] recently published results of a 2-year clinical trial assessing myopia progression with the MiSight lens compared with a control group wearing single-vision spectacles. Although the study used a different control group and different statistical methods for accounting for imbalances between groups at baseline compared with the current study, overall the results of the studies are similar. In the study by Ruiz-Pomeda et al., the mean change in axial length at the 12-month visit was 0.12 mm for the MiSight lens and 0.24 mm for the control group, for a difference in elongation of –0.12 mm. At the 24-month visit, the difference in axial elongation was –0.16 mm (0.28 vs. 0.44 mm). These findings are within the 95% confidence intervals (Table 4) for adjusted axial length differences of this current study (95% confidence intervals, –0.21 to –0.05 [year 1] and –0.30 to –0.14 mm [year 2]).

The current clinical trial used a soft contact lens as the control group. This is in line with the recommendation of the Food and Drug Administration Public Workshop on Controlling the Progression of Myopia.[33] The lenses were matched for all parameters, with the exception of the dual-focus optical design of MiSight. This way, if physiological effects are produced in either a myopic or hyperopic direction, whatever the underlying etiology, they should be identical in the two groups, and thus, any refractive and axial length differences between the two groups can be attributed to the optical design.

The study was conducted in four countries and recruited an ethnically diverse sample. Although myopia progression showed variation among investigational sites, the reduction in myopic progression with MiSight was statistically significant at all sites. Some studies, although not all, have noted a difference in myopia progression as a function of ethnicity.[34–36] This study found no such effect; furthermore, the interaction of lens type with ethnicity or lens type with site when assessing spherical equivalent refraction and axial length progression was not significant, which implies generalizability of the myopia control treatment across different regions and populations.

The high level of wearing time compliance (both hours and days per week) for both groups did not provide sufficient variation to evaluate the effect of wearing time on myopia progression reported by some investigators.[19]

In line with other research, myopia progression varied with age, with younger subjects progressing faster. However, the degree of myopia control with MiSight was not impacted by this factor, suggesting that MiSight works with similar treatment effect in younger and older subjects. A similar finding is observed with sex, where female participants display higher myopia progression than do male participants, also observed by Hyman et al.,[36] but again, the interaction with treatment effect was not significant.

For both refractive error progression and axial elongation, there was a persistence of myopia control effect across the 3 years of the study. The magnitude of the effect was highest in the first year of wear but continued to accrue across the period of observation. In other 2-year studies of myopia control with multifocal soft contact lenses (Table 7), the myopia control effect persisted and accrued over the 2 years.[17,19,20] This is in contrast to the 3-year Correction of Myopia Evaluation Trial (COMET) trial of progressive addition spectacles,[37] where the adjusted treatment effect was 0.18 D with minimal to no accrual in the subsequent 2 years.

A significant proportion of the MiSight group (41%) showed no meaningful progression in spherical equivalent refraction (–0.25 D or less change) over the duration of the trial. In contrast, only 4% of control eyes showed a similar lack of progression (absolute risk reduction, 37%). The number of eyes needed to treat (=1/absolute risk reduction) to achieve this benefit is approximately three eyes (95% confidence interval, 2.1 to 3.6). Therefore, for every three eyes treated in this cohort, one eye will show no meaningful myopic progression over a 3-year period.

Questionnaire responses collected throughout the study align with previous studies[38,39] that have shown that soft contact lenses are well accepted by children. The children in this study showed that they were able to achieve full-time wear, were able to handle the lenses confidently, and had a positive response to contact lens wear. Only one child discontinued for vision quality reasons over the 3-year period. The overall retention rate compares very favorably with previous studies (Table 7).

No serious ocular adverse events were observed during the 3-year clinical trial, including no cases of microbial keratitis. Only four nonsignificant corneal infiltrative events were reported over the 3-year period, all asymptomatic and noted at scheduled visits. The absence of serious or significant ocular adverse events supports the growing acceptance that soft contact lenses are safe for use by children.[40]

Limitations

Enrollment was lower than the target because of recruitment difficulties at some of the sites; however, subject retention was high, and the sample size was sufficiently large to show differences between the two lens types for the primary efficacy end point of 0.75 D at 3 years.

Subjects in this clinical trial were not withdrawn from treatment to assess the extent to which the benefit is sustained. Some myopia treatments with atropine have been shown to be susceptible to post-treatment acceleration.[41] Finally, the investigators had access to the

randomization codes. Although these randomization codes were only identified as "lens A" and "lens B," theoretically an examiner could have identified whether lens A was the experimental or control assignment.

Summary

This 3-year randomized clinical trial, designed to evaluate the safety and effectiveness of a soft contact lens intended to slow myopia progression in children, demonstrates the following:

- The progression of refractive error in children is significantly reduced by the MiSight lens compared with a single-vision soft contact lens.
- The axial elongation that underlies and is correlated with refractive error progression is significantly less with the MiSight lens compared with a single-vision soft contact lens.
- No safety concerns were evident for this population of children who started daily disposable soft contact lens wear between 8 and 12 years of age.
- The high subject retention, long wearing time, and favorable subjective ratings show that contact lens acceptance was sustained across 3 years. This work supports previous findings[38,39] that soft contact lenses are well accepted by children. Children as young as 8 years are able to achieve full-time wear, handle the lenses confidently soon after initial fitting, and achieve good comfort.

ARTICLE INFORMATION

Submitted: June 14, 2018

Accepted: March 25, 2019

Funding/Support: The study was sponsored by CooperVision Inc. No additional funding was received by the investigator or CRO.

Conflict of Interest Disclosure: PC is an employee of the sponsor. The sponsor participated in study design, analysis, and interpretation. The authors were responsible for preparation of this article and the decision to submit this article for publication. The contract research organization had full access to the study data; the investigators had partial access to the study data and take full responsibility for their presentation in this article.

Study Registration Information: This study is registered on ClinicalTrials.gov (identifier NCT01729208).

Author Contributions: Conceptualization: PC, NSL; Formal Analysis: PC, GY; Investigation: SCP-d-M, NSL, CN, DJ; Project Administration: PC, GY; Writing – Original Draft: PC; Writing – Review & Editing: PC, SCP-d-M, NSL, CN, DJ, GY.

Acknowledgments

CooperVision, Inc.

Paul Chamberlain, John McNally, Stuart Cockerill, Janice Tarrant, Percy Lazon de la Jara, Wenjuan Feng

Visioncare Research Ltd.

Graeme Young (Medical Monitor); Chris Hunt (Statistician); Ruth Craven (Clinical Research Manager); Susanna Jones (Project Manager); Michael Spyridon, Tom Boyes, Sarah McCready, Kristina Roslin (Clinical Research Associates); Shaun Peters (Clinical Research Coordinator); Tricia Riley, Emma Lyle, Glenis Rogers, Janet Faulks (Data Entry)

University of Minho, CEOR Lab

José Manuel González-Méijome (Principal Investigator); Sofia Cláudia Peixoto-de-Matos, Ana Maria Fernandes de Pinho Dias, Helena Isabel Ferreira-Neves, Daniela Patricia Lopes-Ferreira, Ana Amorim-de-Sousa (Coinvestigators)

Aston University Ophthalmic Research Group

Nicola Logan (Principal Investigator); Susie Jones, Fi Cruickshank, Manbir Nagra (Coinvestigators)

National University Health System, Ophthalmology Department, Singapore

Seang Mei Saw (Chief Investigator); Cheryl Ngo (Principal Investigator 2014 to current, Coinvestigator 2012 to 2014); Inez By Wong (Principal Investigator, 2012 to 2014); Ivy Law (Administrative Manager); Ray Manotosh, Michelle Lim, Amanda Lim (Coinvestigators); Anny Leow (Coordinator)

University of Waterloo School of Optometry, Waterloo, Canada

Lyndon Jones (Principal Investigator); Debbie Jones, Jill Woods Lindsay Paquette, Mike Yang, Karen Walsh (Coinvestigators); Jane Johnson, Marina Simpson, Leona Voss, Debbie Murray, Amanda McIntosh (Assistants)

Consultant

Mark A. Bullimore

REFERENCES

1. Vitale S, Ellwein L, Cotch MF, et al. Prevalence of Refractive Error in the United States, 1999–2004. Arch Ophthalmol 2008;126:1111–9.
2. Lee YY, Lo CT, Sheu SJ, et al. What Factors Are Associated with Myopia in Young Adults? A Survey Study in Taiwan Military Conscripts. Invest Ophthalmol Vis Sci 2013;54:1026–33.
3. Lin LL, Shih YF, Tsai CB, et al. Epidemiologic Study of Ocular Refraction among Schoolchildren in Taiwan in 1995. Optom Vis Sci 1999;76:275–81.
4. Wu HM, Seet B, Yap EP, et al. Does Education Explain Ethnic Differences in Myopia Prevalence? A Population-based Study of Young Adult Males in Singapore. Optom Vis Sci 2001;78:234–9.
5. Risk Factors for Idiopathic Rhegmatogenous Retinal Detachment. The Eye Disease Case-control Study Group. Am J Epidemiol 1993;137:749–57.
6. Mitchell P, Hourihan F, Sandbach J, et al. The Relationship between Glaucoma and Myopia: The Blue Mountains Eye Study. Ophthalmology 1999;106:2010–5.
7. Lim R, Mitchell P, Cumming RG. Refractive Associations with Cataract: The Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 1999;40:3021–6.
8. Vongphanit J, Mitchell P, Wang JJ. Prevalence and Progression of Myopic Retinopathy in an Older Population. Ophthalmology 2002;109:704–11.
9. Vitale S, Schein OD, Meinert CL, et al. The Refractive Status and Vision Profile: A Questionnaire to Measure Vision-related Quality of Life in Persons with Refractive Error. Ophthalmology 2000;107:1529–39.
10. Hays RD, Mangione CM, Ellwein L, et al. Psychometric Properties of the National Eye Institute–Refractive Error Quality of Life Instrument. Ophthalmology 2003;110:2292–301.
11. Bailey MD, Olson MD, Bullimore MA, et al. The Effect of LASIK on Best-corrected High- and Low-contrast Visual Acuity. Optom Vis Sci 2004;81:362–8.
12. Cho P, Cheung SW. Retardation of Myopia in Orthokeratology (Romio) Study: A 2-year Randomized Clinical Trial. Invest Ophthalmol Vis Sci 2012;53:7077–85.
13. Cho P, Cheung SW, Edwards M. The Longitudinal Orthokeratology Research in Children (Loric) in Hong Kong: A Pilot Study on Refractive Changes and Myopic Control. Curr Eye Res 2005;30:71–80.
14. Walline JJ, Jones LA, Sinnott LT. Corneal Reshaping and Myopia Progression. Br J Ophthalmol 2009;93:1181–5.
15. Anstice NS, Phillips JR. Effect of Dual-focus Soft Contact Lens Wear on Axial Myopia Progression in Children. Ophthalmology 2011;118:1152–61.
16. Sankaridurg P, Holden B, Smith E, 3rd, et al. Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-year Results. Invest Ophthalmol Vis Sci 2011;52:9362–7.
17. Walline JJ, Greiner KL, McVey ME, et al. Multifocal Contact Lens Myopia Control. Optom Vis Sci 2013;90:1207–14.
18. Fujikado T, Ninomiya S, Kobayashi T, et al. Effect of Low-addition Soft Contact Lenses with Decentered Optical Design on Myopia Progression in Children: A Pilot Study. Clin Ophthalmol 2014;8:1947–56.
19. Lam CS, Tang WC, Tse DY, et al. Defocus Incorporated Soft Contact (Disc) Lens Slows Myopia Progression in Hong Kong Chinese Schoolchildren: A 2-year Randomised Clinical Trial. Br J Ophthalmol 2014;98:40–5.
20. Paune J, Morales H, Armengol J, et al. Myopia Control with a Novel Peripheral Gradient Soft Lens and Orthokeratology: A 2-year Clinical Trial. Biomed Res Int 2015;2015:507572.
21. Aller TA, Liu M, Wildsoet CF. Myopia Control with Bifocal Contact Lenses: A Randomized Clinical Trial. Optom Vis Sci 2016;93:344–52.
22. Cheng X, Xu J, Chehab K, et al. Soft Contact Lenses with Positive Spherical Aberration for Myopia Control. Optom Vis Sci 2016;93:353–66.
23. Ruiz-Pomeda A, Perez-Sanchez B, Valls I, et al. MiSight Assessment Study Spain (MASS). A 2-Year Randomized Clinical Trial. Graefes Arch Clin Exp Ophthalmol 2018;256:1011–21.
24. Allen PM, Radhakrishnan H, Price H, et al. A Randomised Clinical Trial to Assess the Effect of a Dual Treatment on Myopia Progression: The Cambridge

Anti-Myopia Study. Ophthalmic Physiol Opt 2013; 33:267–76.

25. Smith EL, 3rd, Hung LF, Arumugam B. Visual Regulation of Refractive Development: Insights from Animal Studies. Eye (Lond) 2014;28:180–8.

26. Liu Y, Wildsoet C. The Effect of Two-zone Concentric Bifocal Spectacle Lenses on Refractive Error Development and Eye Growth in Young Chicks. Invest Ophthalmol Vis Sci 2011;52:1078–86.

27. Liu Y, Wildsoet C. The Effective Add Inherent in 2-zone Negative Lenses Inhibits Eye Growth in Myopic Young Chicks. Invest Ophthalmol Vis Sci 2012;53: 5085–93.

28. Arumugam B, Hung LF, To CH, et al. The Effects of Simultaneous Dual Focus Lenses on Refractive Development in Infant Monkeys. Invest Ophthalmol Vis Sci 2014;55:7423–32.

29. Benavente-Perez A, Nour A, Troilo D. The Effect of Simultaneous Negative and Positive Defocus on Eye Growth and Development of Refractive State in Marmosets. Invest Ophthalmol Vis Sci 2012;53: 6479–87.

30. Arumugam B, Hung LF, To CH, et al. The Effects of the Relative Strength of Simultaneous Competing Defocus Signals on Emmetropization in Infant Rhesus Monkeys. Invest Ophthalmol Vis Sci 2016;57: 3949–60.

31. Tse DY, Lam CS, Guggenheim JA, et al. Simultaneous Defocus Integration During Refractive Development. Invest Ophthalmol Vis Sci 2007;48: 5352–9.

32. McFadden SA, Tse DY, Bowrey HE, et al. Integration of Defocus by Dual Power Fresnel Lenses Inhibits Myopia in the Mammalian Eye. Invest Ophthalmol Vis Sci 2014;55:908–17.

33. Walline JJ, Robboy MW, Hilmantel G, et al. Food and Drug Administration, American Academy of Ophthalmology, American Academy of Optometry, American Association for Pediatric Ophthalmology and Strabismus, American Optometric Association, American Society of Cataract and Refractive Surgery, and Contact Lens Association of Ophthalmologists Co-sponsored Workshop: Controlling the Progression of Myopia: Contact Lenses and Future Medical Devices. Eye Contact Lens 2018; 44:205–11.

34. Saw SM, Tong L, Chua WH, et al. Incidence and Progression of Myopia in Singaporean School Children. Invest Ophthalmol Vis Sci 2005;46:51–7.

35. French AN, Morgan IG, Burlutsky G, et al. Prevalence and 5- to 6-year Incidence and Progression of Myopia and Hyperopia in Australian Schoolchildren. Ophthalmology 2013;120:1482–91.

36. Hyman L, Gwiazda J, Hussein M, et al. Relationship of Age, Sex, and Ethnicity with Myopia Progression and Axial Elongation in the Correction of Myopia Evaluation Trial. Arch Ophthalmol 2005;123: 977–87.

37. Gwiazda J, Hyman L, Hussein M, et al. A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children. Invest Ophthalmol Vis Sci 2003;44: 1492–500.

38. Walline JJ, Jones LA, Sinnott L, et al. Randomized Trial of the Effect of Contact Lens Wear on Self-perception in Children. Optom Vis Sci 2009; 86:222–32.

39. Walline JJ, Gaume A, Jones LA, et al. Benefits of Contact Lens Wear for Children and Teens. Eye Contact Lens 2007;33:317–21.

40. Bullimore MA. The Safety of Soft Contact Lenses in Children. Optom Vis Sci 2017;94:638–46.

41. Chia A, Chua WH, Wen L, et al. Atropine for the Treatment of Childhood Myopia: Changes after Stopping Atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol 2014;157:451–7 e1.

3.4. Additional Analyses from the 3-year trial

At the conclusion of this three-year trial, cycloplegic auto-refraction measurements showed a progressive slowing of myopia in the dual-focus treated population. The unadjusted spherical equivalent refractive error (SERE) reduction was 0.40D after year 1, 0.54D after year 2, and 0.73D at the study's conclusion. After adjusting for covariates outlined in the statistical plan, the estimated mean three-year progression was –0.65D in MiSight-treated eyes compared to –1.31D in control eyes ($p<0.0001$). Despite these positive results, the study narrowly missed the target of 0.75D reduction, whether assessed using raw unadjusted means or the adjusted values from a linear mixed model which accounted for differences between control and treatment groups of potential covariates unrelated to treatment.

However, neither the methodological differences nor the small shortfall from the target represent a clinically significant margin. It is essential to interpret these findings in the context of clinical quantization, where refractive changes are typically measured in 0.25D steps using trial lenses or a phoropter. In contrast, refractive error measurements in this study were:

a. Performed under cycloplegia, and
b. Assessed using an open-field auto-refractor with a resolution of 0.01D.

This higher-resolution measurement differs from what is typically used in clinical practice, where refractions are generally conducted in 0.25D increments using a phoropter or trial lenses. To align with standard clinical assessments, the study also included manifest refraction measurements. The mean change in manifest refraction was –0.53±0.62D in MiSight-treated eyes compared to –1.29±0.70D in control eyes, resulting in a 0.76D difference. This suggests that the observed reduction in refractive error progression is clinically meaningful and aligns closely with the gold standard outcomes reported in the three-year manuscript.

Additionally, this study provided an opportunity to compare refractive error measurements with and without cycloplegia, with the former serving as the primary endpoint in the earlier manuscript. Figure 5 illustrate the data at baseline and the three-year follow-up, respectively. The most striking observation is the clear divergence in SERE between the treated and control eyes over time. The strong correlation ($R^2 = 0.88$) across all refraction levels in both groups indicates that a well-conducted manifest refraction can serve as a reliable measure of myopia progression—even in the absence of time-consuming cycloplegic refraction or an optical biometer.

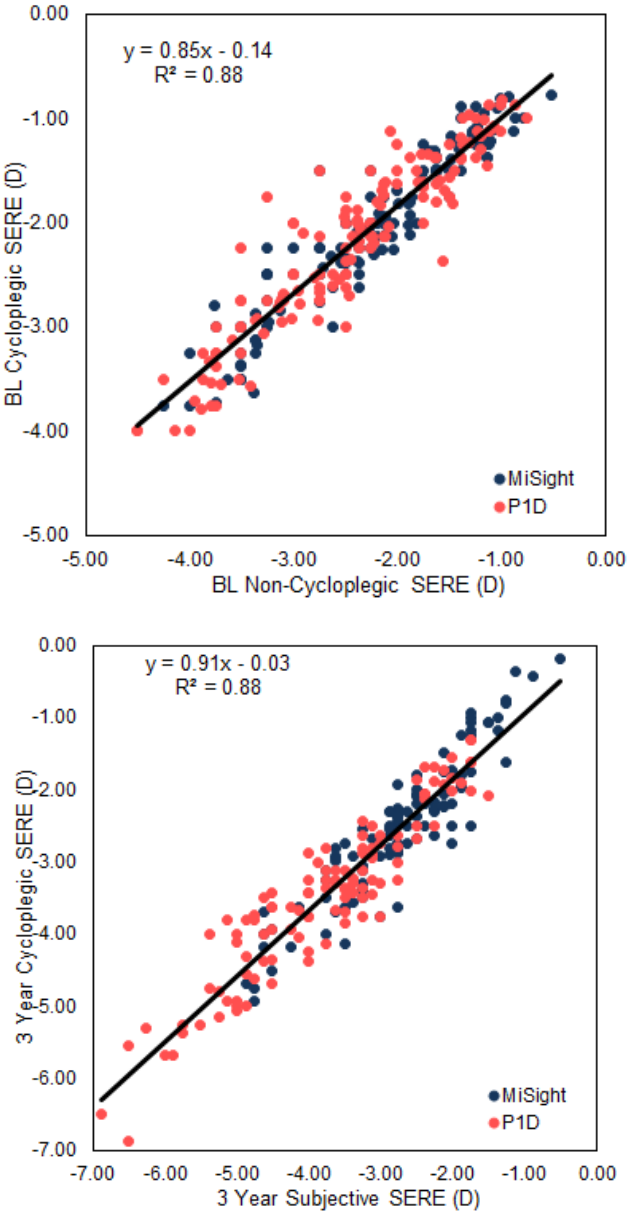


Figure 5: Scatterplot showing the correlation between spherical equivalent non-cycloplegic and cycloplegic autorefraction at baseline (A; n=288 eyes) and at 3 years (B; n=216 eyes). Eyes in the treated (blue) and control (red) groups had almost identical SEs at baseline

3.5. Myopia Control effect across the population

Although the randomized controlled trial provides an unbiased estimate of the average treatment effects, this study design cannot reveal treatment effects of individual subjects because the control and treatment cohorts are composed different individual eyes. For example, the faster growing treated eyes, could reflect slowed growth of eyes that if left untreated would have experienced even faster accelerated growth, or a failure of treatment in those eyes. In spite of this limitation, distributions of growth and progression (Figure 6 here and Figure 3 in publication) have been examined and the similarity of treated and control eye distribution standard deviations has been interpreted as evidence of a fixed treatment effect for all eyes. (Brennan, Toubouti et al. 2020, Charman and Radhakrishnan 2021) However, the analysis these authors employed is based upon an assumption of a unimodal gaussian distribution (with a single SD). The data from the MiSight 3-year trial (Figure 6) clearly show

an indication that the treated eye axial elongation population was not normally distributed. Normalcy of distributions is most easily seen when plotting the data as q-q plots.

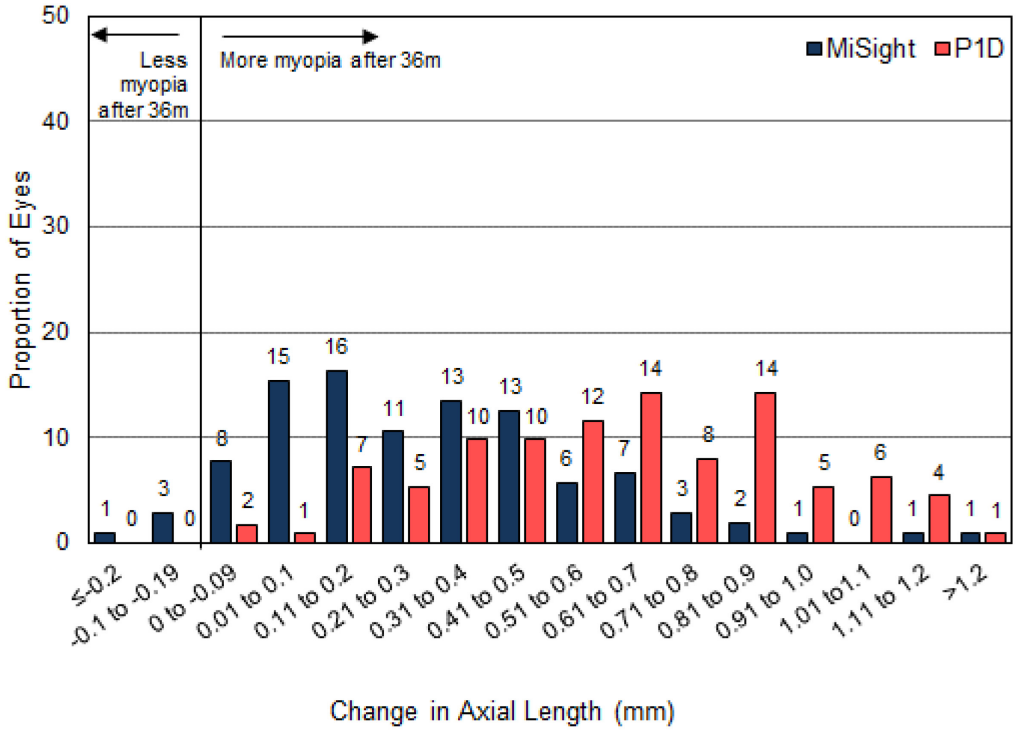


Figure 6: Frequency distribution of change in axial length from baseline to 36 months. The navy and red bars represent MiSight and control groups respectively.

Figure 7 shows q-q plots for 3-year progression of SE and axial elongation for the MiSight and Proclear groups. Vertical separation and approximate linearity of the functions reveal the treatment effect and the approximate logistic distribution of the results. Notably, the faster progressing and faster growing treated eyes converge with the progression and growth of the faster growing control eyes, which is consistent with the notion that these faster progressing treated eyes are in fact not responding to the treatment intervention.

Do all treated subjects, including fast and slow progressors receive an identical treatment benefit? The current clinical trial data cannot answer this question as no evidence of prior progression for these subjects are available. A more direct way to assess treatment effects in individual eyes is to track growth and progression of the same eyes prior to treatment and then once treatment has begun.

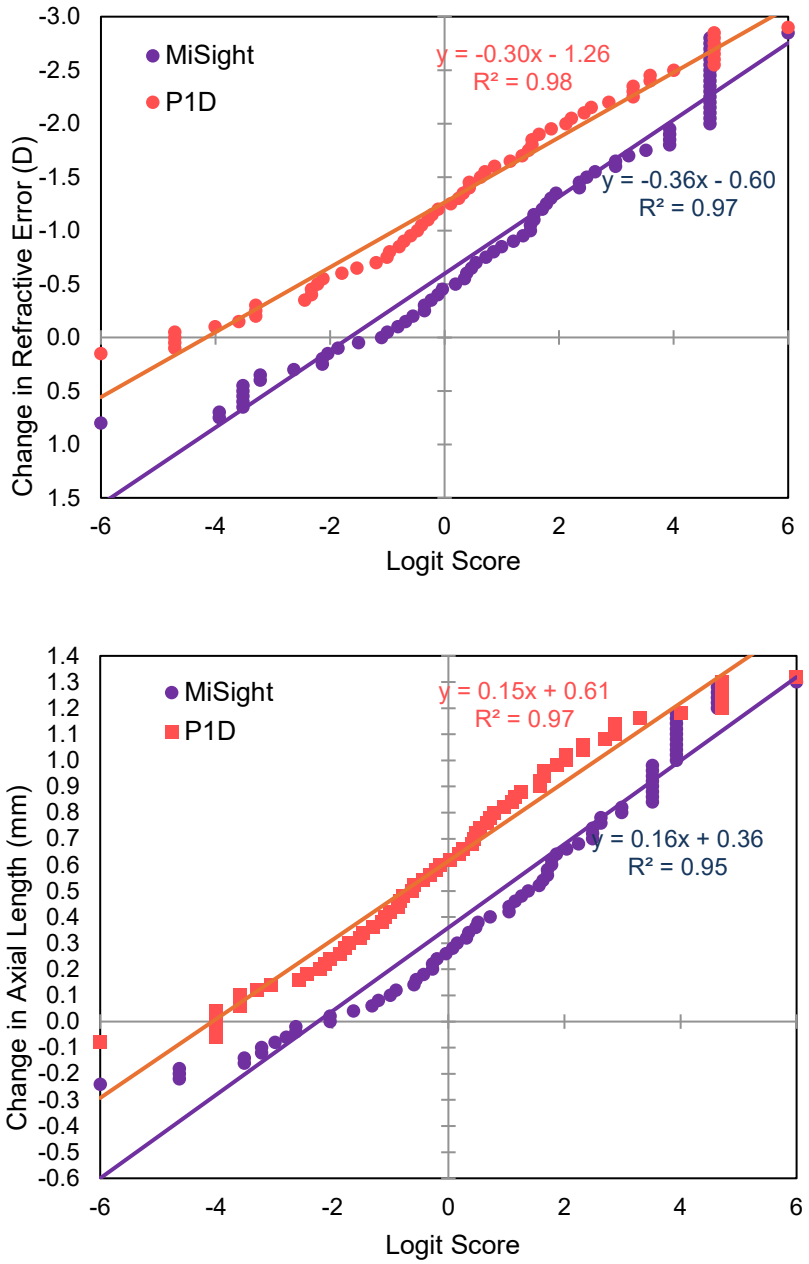


Figure 7: QQ plots for the treated (blue) and control (red) eyes. Changes from baseline to 36 months for SE (top) and axial length (bottom) are plotted as a function of ordered logit scores.

3.6. Additional factors explored for influence on treatment effect.

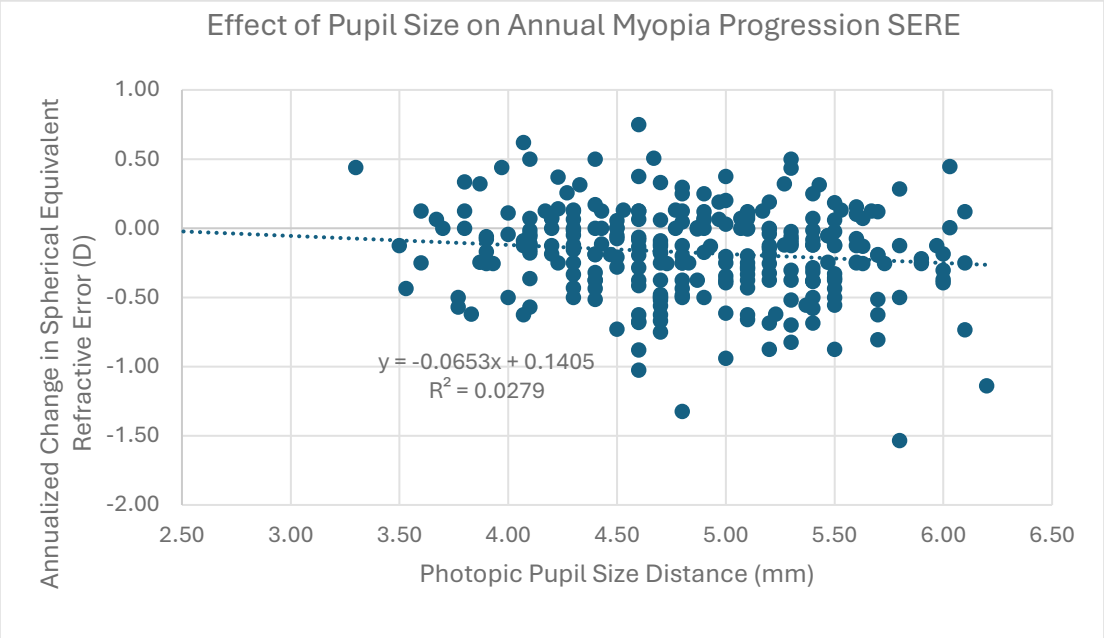
Small differences in covariates between the control and treatment groups offered an opportunity to assess whether age group (8-10;11-12), sex, site or baseline myopia affected the treatment effect. None of these factors were significant contributors to the treatment effect. The possible impact of an additional two factors (pupil size and wear-time), that were not part of the original linear mixed model analysis were also explored. Each of these factors could influence the efficacy of the myopia control intervention.

Pupil size

Experience with concentrically designed multifocal contact lenses that provide increased depth of focus for presbyopic patients have established that pupil size can have a dramatic impact on the image quality which, although still a factor, is less so for designs with multiple

annular zones, (Young, Grey et al. 1990, Bradley, Nam et al. 2014) Young eyes generally exhibit larger pupils than older presbyopic eyes,(Winn, Whitaker et al. 1994) and individual eyes can have different pupil sizes at any light level. As discussed in Chapter 2 larger pupils can expose greater amounts of defocus in eyes fit with concentrically designed multifocal contact lenses or in treated OrthoK eyes.(Faria-Ribeiro, Navarro et al. 2016, Ji, Yoo et al. 2018) Evidence of enhanced slowing of myopia in OrthoK-treated eyes as a function of pupil size has been reported, but this result does not appear to be universal.(Chen, Niu et al. 2012, Huang, Zhao et al. 2023, Guo, Zhang et al. 2024) As illustrated in Chapter 2 Figures 2&3, the MiSight design provided alternating zones of defocus and correcting zones to minimize dependency of the myopia control effect on pupil size.

In the current clinical trial, pupil size was measured at all follow up visits with the Neuroptic pupilometer. Progression rates and axial growths were on average slightly greater with larger pupil sizes (-0.07D per mm and +0.03mm per mm of pupil diameter), but pupil size accounted for between 3 and 6 % of the data variance suggesting that pupil size has a minor or zero effect on growth and progression during treatment. It is important to emphasize that single measures of pupil diameter in the clinic may be poor indicators of the chronic pupil sizes encountered by each subject during their daily lives.



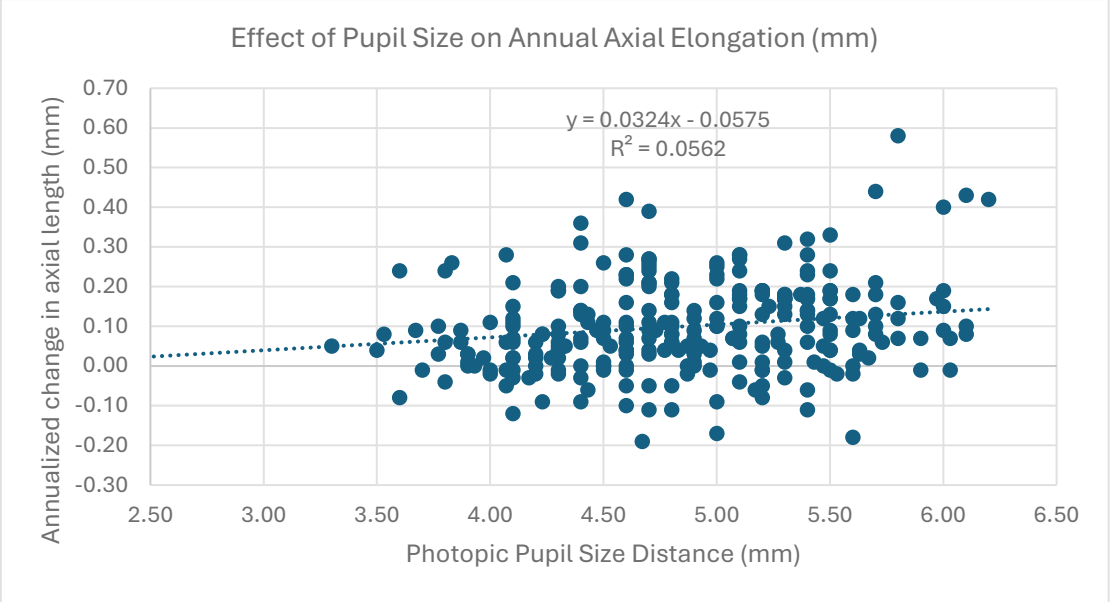


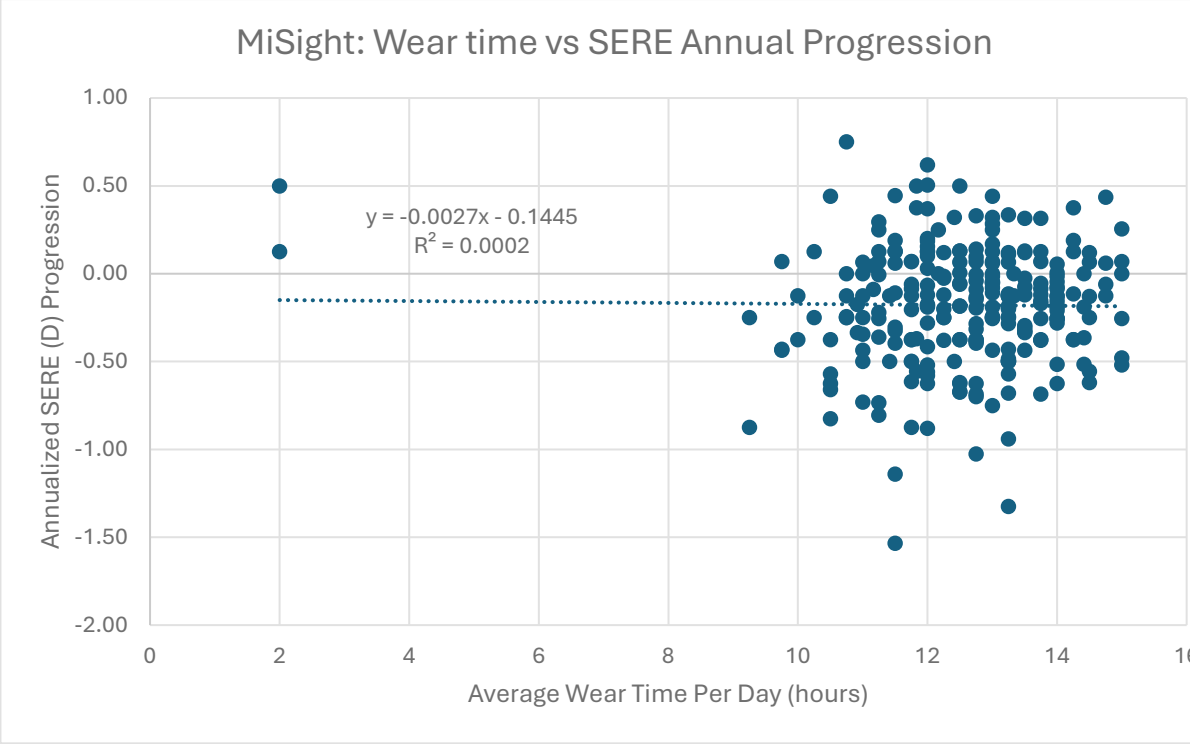
Figure 8: Scatter plots of changes in SE (top) and axial length (bottom) from baseline to 36 months as a function of the measured photopic pupil diameters.

Wear-time

Wear time compliance was another factor considered important to collect and analyze in relation to in myopia progression in the treated eyes. In this trial, with the protocol initiated in 2011, compliance was assessed by the administration of a questionnaire. Central to this analysis was the collection of data from individual subjects related to wear time, both in terms of days per week and hours per day. Each of these factors were assessed separately for both weekdays and weekends and at each follow up visit, which after an initial period of visits settled to a cadence of 6 monthly intervals. To reduce potential for bias, subjects were not asked to state hours per day of wear, but rather recall the typical hour and minute of lens application and removal.

Studies of myopia control in other specially designed contact lenses for myopia control intervention have collected wear time information and these studies reported that reduced wear time linked with greater myopia progression in treated eyes. (Lam, Tang et al. 2014, Sankaridurg, Bakaraju et al. 2019) Figure 9 reports myopia progression and eye growth against average daily wear time (hours per day) collected individually for weekdays and weekends at each annual visit during this study.

No correlation was observed between average wear time and the annualized progression of myopia, as measured by spherical equivalent refractive error (SERE) or axial length (AL). This is evidenced by the flat regression line and a very low R-squared value. The outlier data point, an average wear time of 2 hours per day, was from a single subject in the first year of the study who exhibited poor lens wear compliance. Notably, in years 2 and 3 of the MIST-401 study, this subject wore the lens for an average of 13 and 14 hours per day, respectively. Overall, there was no association between wear time and myopia progression or axial elongation in the treated eye group.



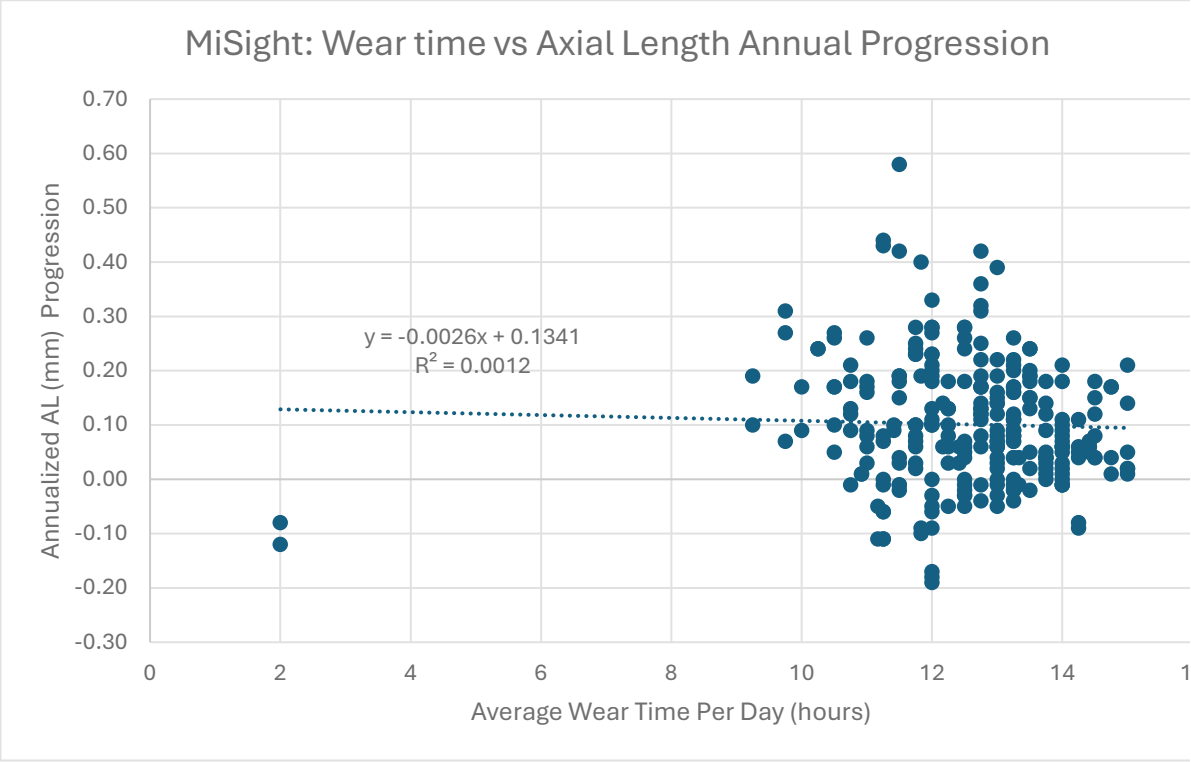


Figure 9: Scatter plots of annual changes in SE (top) and axial length (bottom) as a function of the reported average daily wear time at each annual follow up visit.

The absence of significant correlations between measured covariates—pupil size and wear time suggests that other factors play a more dominant role in influencing myopia progression and eye growth. This lack of association may stem from the careful design considerations discussed earlier in this thesis. The treatment optics were meticulously engineered to maintain a balance between correction and treatment optics across a range of pupil sizes

while preserving normal accommodative response. Additionally, the daily disposable modality, along with high compliance in wear time, may reflect either the ease of lens use or the quality of instructions and monitoring provided by study sites.

As outlined in the published findings, several other covariates also had no significant impact on treatment effect. These included baseline age group (8-10 vs. 11-12 years), sex, and ethnicity. The only variable that showed a significant interaction with treatment effect was visit number, though this time-based factor may inherently correlate with age. The lack of a direct age effect may be explained by the overlapping age ranges of participants over the three-year study period, which likely minimized age-related differences.

These findings provide compelling evidence of the generalizability of the treatment effect observed in the first three years. The consistency across different demographic groups reinforces the broad applicability of this intervention and offers a strong foundation for future research.

The first phase of this trial demonstrated that dual-focus soft contact lenses are an effective strategy for slowing myopia progression over a three-year period, offering clinically meaningful benefits for children at risk of developing high myopia. However, since myopia progression does not abruptly stop after childhood, it became clear that further investigation was necessary to assess the long-term sustainability of these effects.

CHAPTER 4: A 6-YEAR RANDOMIZED CLINICAL TRIAL OF MISIGHT LENSES FOR MYOPIA CONTROL

4.1. Background and study design

The MiSight study was the first randomized clinical trial of a soft contact lens for myopia control to extend beyond two years. At the time of completion and publication, only one other study had examined myopia progression beyond this duration. (Hiraoka, Kakita et al. 2012) However, that study did not employ strict randomization, as participants could choose whether to be in the treatment group. In contrast, the MiSight trial was pioneering in providing the first randomized, controlled evidence of a sustained ability to slow myopic eye growth over multiple years. The results showed that eye growth was slowed across both major ethnic groups enrolled in the study—Asian and Caucasian—and in both younger and older age groups, offering encouraging evidence that dual-focus contact lenses could be an effective intervention for a broad population.

While these findings were promising, several critical questions remained. Myopia can progress from early childhood through young adulthood, raising the question of whether the slowed growth and progression observed in the trial could be further sustained throughout the natural course of myopia development. Additionally, it was unclear whether continuing treatment into the teenage years would maintain the benefits observed in younger children. These uncertainties led to the decision to extend the study for an additional three years to explore two primary hypotheses: that slowed eye growth in the original treatment group would persist if treatment was maintained, and that contact lenses would remain safe and effective for myopic children as they transitioned into adolescence.

A direct continuation of the placebo-controlled study, however, was not considered ethical or feasible. The informed consent process at the start of the original trial had clearly stated that the study would last for three years, meaning any extension required a new consent process. Since the treatment's efficacy had already been demonstrated, it was unlikely that families would accept a 50% chance of continued monitoring in an untreated placebo group, which could lead to significant retention issues. Practical concerns further complicated the situation, as the treatment lens had by this point become commercially available in the countries where the trial was conducted. Given these challenges, it was determined that the best path forward was to modify the study design.

For Part 2 of the trial (Years 4-6), all participants from the original cohort were invited to continue in an open-label study, in which all eyes would receive treatment. The study lens supply was transitioned to a commercial lot number system, simplifying inventory management. This design shift eliminated the placebo group, but it also created new opportunities and challenges. By the conclusion of Part 2, participants would be between the ages of 14 and 18, allowing researchers to observe a substantial portion of the natural progression of juvenile-onset myopia.

Without a concurrent randomized control group, the standard approach of comparing mean control and mean treated eyes was no longer available. Instead, the study focused on five key research questions.

1. Would slowed average growth and progression observed in the treated cohort during years 1-3 be maintained during the additional 3 years of treatment? (compare growth of original treated cohort during years 1-3 with that observed during years 4-6)
2. Would axial growth in eyes from the original control cohort slow significantly once treatment was initiated? (compare growth of the original control cohort during years 1-3 with that observed during years 4-6)
3. Would prior treatment or absence of treatment affect the treatment magnitude? (compare growth and progression during years 4-6 between the original control group and the original treatment group)
4. Could the MiSight myopia control contact lens slow axial growth and myopia progression for those eyes that were faster or slower progressing prior to treatment

(during years 1-3)? (Compare change in growth and progression of individual eyes between years 1-3 and years 4-6).

5. Could switching the initial control eyes from single vision lenses to myopia control treatment lenses have the potential to identify those eye/subjects who do not respond to treatment? (Compare growth and progression of individual eyes between years 1-3 and years 4-6)

4.2. Publication: Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial

CLINICAL TRIAL

Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial

Paul Chamberlain, BSc,[1]* Arthur Bradley, PhD,[1] Baskar Arumugam, PhD, FAAO,[1] David Hammond, PhD,[1] John McNally, OD, FAAO,[1] Nicola S. Logan, PhD,[2] Deborah Jones, BSc, FAAO,[3] Cheryl Ngo, MBBS, Mmed,[4] Sofia C. Peixoto-de-Matos, MSc,[5] Chris Hunt, MSc,[6] and Graeme Young, PhD, FAAO[6]

SIGNIFICANCE: Treatment of myopic children with a dual-focus soft contact lens (DFCL; MiSight 1 day) produced sustained slowing of myopia progression over a 6-year period. Significant slowing was also observed in children switched from a single vision control to treatment lenses (3 years in each lens).

PURPOSE: This study aimed to evaluate the effectiveness of DFCLs in sustaining slowed progression of juvenile-onset myopia over a 6-year treatment period and assess myopia progression in children who were switched to a DFCL at the end of year 3.

METHODS: Part 1 was a 3-year clinical trial comparing DFCLs with a control contact lens (Proclear 1 day) at four investigational sites. In part 2, subjects completing part 1 were invited to continue for 3 additional years during which all children were treated with MiSight 1 day DFCLs (52 and 56 from the initially treated [T6] and control [T3] groups, respectively). Eighty-five subjects (45 [T3] and 40 [T6]) completed part 2. Cyclopleged spherical equivalent refractive errors (SEREs) and axial lengths (ALs) were monitored, and a linear mixed model was used to compare their adjusted change annually.

RESULTS: Average ages at part 2 baseline were 13.2 ± 1.3 and 13.0 ± 1.5 years for the T6 and T3 groups, respectively. Slowed myopia progression in the T6 group observed during part 1 was sustained throughout part 2 (mean ± standard error of the mean: change from baseline SERE [in diopters], −0.52 ± 0.076 vs. −0.51 ± 0.076; change in AL [in millimeters], 0.28 ± 0.033 vs. 0.23 ± 0.033; both $P > .05$). Comparing progression rates in part 2 for the T6 and T3 groups, respectively, indicates that prior treatment does not influence efficacy (SERE, −0.51 ± 0.076 vs. −0.34 ± 0.077; AL, 0.23 ± 0.03 vs. 0.18 ± 0.03; both $P > .05$). Within-eye comparisons of AL growth revealed a 71% slowing for the T3 group (3 years older than part 1) and further revealed a small subset of eyes (10%) that did not respond to treatment.

CONCLUSIONS: Dual-focus soft contact lenses continue to slow the progression of myopia in children over a 6-year period revealing an accumulation of treatment effect. Eye growth of the initial control cohort with DFCL was slowed by 71% over the subsequent 3-year treatment period.

Optom Vis Sci 2022;99:204–212. doi:10.1097/OPX.0000000000001873

OPEN

Author Affiliations:
[1]CooperVision Inc., Pleasanton, California
[2]Ophthalmic Research Group, School of Optometry, Aston University, Aston Triangle, Birmingham, United Kingdom
[3]Centre for Ocular Research and Education, School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada
[4]Department of Ophthalmology, National University Hospital, Singapore, Singapore
[5]Clinical and Experimental Optometry Research Lab, Centre of Physics, School of Sciences, University of Minho, Braga, Portugal
[6]Visioncare Research Ltd., Farnham, Surrey, United Kingdom
*pchamberlain@coopervision.com

Myopia is predicted to affect more than half of the world's population by 2050,[1] and the prevalence of high myopia (defined as myopic refractive errors higher than −6 D)[2] is also increasing, being present in approximately 3% of the myopic population in 2000 and expected to reach 10% by 2050. The associated retinal and specifically macula pathologies, such as myopic macular degeneration,[3,4] are already leading causes of impaired vision in Europeans younger than 75 years[5] and have become the leading cause of blindness in older Chinese populations.[6]

Although the prevalence of retinal pathologies associated with myopic eye growth increases later in life,[7] the excessive eye growth that results in myopia often begins early in childhood[8] and continues into adolescence.[9] The anomalous growth of the eye can continue over many years[10] and can vary widely in rate—for example, from 0.17 mm to a maximum reported 0.53 mm per year in European children[11]—with earlier onset and faster progression generally resulting in higher levels of adult myopia.[12]

Efforts to delay onset of myopia and slow myopia progression have included modifying a child's visual environment, for example, increased lighting,[13] increased time outdoors,[14–16] and manipulations of visual optics to counteract the external environmental changes. Optical interventions incorporated into soft contact lenses, spectacle lenses, and orthokeratology are designed to introduce some myopic defocus and have shown promise in slowing eye growth.[17]

Assessing the efficacy of myopia control treatments is complicated by the need to monitor eye growth and refractive error over an extended period,[18] coupled with the significant covariate of slowed myopic eye growth with increasing age.[12] The added impact of measurement noise and selection bias may compromise the value of short-term studies.[19] Also, short-duration trials cannot examine important questions of treatment sustainability or satisfactorily reveal the interactions of treatment duration and age. In contrast, longer-term myopia control trials can be expected to evaluate sustained treatment effectiveness, whereas normal age-related

slowing of progression is ongoing during the evaluation period. However, maintaining control groups over long periods without treatment raises ethical and practical considerations.[20,21] Only a few 3-year randomized controlled clinical trials of optical myopia management have been published.[22–25] This is the first study to report myopia control efficacy data in a study cohort over a 6-year period.

After an observed average reduction of –0.73 D in myopia progression over the 3-year part 1 of this randomized control trial,[22] the dual-focus contact lens myopia management option was approved by the U.S. Food and Drug Administration[26] for the indication of slowing the progression of myopia in children. During part 1, standard treatment and control arms were used. However, because of ethical concerns,[20,21] the almost zero chance of placebo effect influencing the data,[27,28] and concerns that families would simply choose to purchase the commercially available treatment lens, subjects from the part 1 control group were all switched into the treatment lens at the start of year 4 (part 2). This protocol shift would enable better retention of subjects. The spherical equivalent refractive error and axial length progression data for both groups during part 2 (years 4 to 6) and the full 6 years of the trial were used to test the following hypotheses: (1) the slowed growth observed during years 1 to 3 in the treatment group would be sustained during years 4 to 6; (2) prior treatment for a period of 3 years will not result in faster progression compared with a newly treated group of the same age; (3) slowed myopia progression is achieved when treatment is initiated in an older cohort of subjects; and (4) faster growing eyes experience greater slowing of growth during treatment.

METHODS

Part 1 of this multicenter, double-masked, randomized, controlled clinical trial (ClinicalTrials.gov identifier, NCT01729208) compared myopia progression and eye growth in children aged 8 to 12 years at baseline and fitted with either a daily disposable dual-focus myopia control soft contact lens (MiSight 1 day, omafilcon A; CooperVision, Inc., Pleasanton, CA) or a standard single-vision, daily disposable lens (Proclear 1 day, omafilcon A; CooperVision, Inc.). The duration of part 1 was 3 years. Part 2 of the clinical trial was an open-label study with no masking or randomization, as all subjects were refitted with the dual-focus treatment lenses. Subjects remained masked to their previous cohort assignment for part 1. Part 2 was 3 years in duration and registered under the same identifier. Both parts of the study were conducted at the same four investigational sites: University of Minho, Braga, Portugal; Aston University, Birmingham, United Kingdom; National University Hospital, Singapore; and the University of Waterloo, Ontario, Canada. The study was conducted in conformance with the ethical principles in the Declaration of Helsinki, with the International Council for Harmonization guidelines for Good Clinical Practice and all applicable local regulations. This research was reviewed by an independent ethical review board and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research. Standardized measurements were used across sites, under the same protocol with identical equipment calibration instructions to ensure concordance across the study sites.[22] All subjects who successfully completed part 1 were invited to enroll in part 2. Initial visits for part 2 took place immediately after the 36-month exit visit and reconsent. These visits were completed between December 2015 and February 2017.

An assent document was explained to, read, and signed by each potential study subject before enrollment in each part of the study. Similarly, an informed consent document was explained to, read, understood, and signed by a parent or legal guardian of the subject before enrollment.

During the 3-year part 1, cohorts were identified as "control" and "treatment" groups and monitored every 6 months as reported previously.[22] In part 2, however, both cohorts from part 1 received the same treatment lens. Thus, these two cohorts are referred to as T6 (for those children who received 6 years of dual-focus myopia control treatment lenses) and T3 (for the original control group who then received 3 years of treatment in dual-focus myopia control treatment lenses at a later age). Subjects were subsequently monitored in part 2 at 42-, 48-, 54-, 60-, 66-, and 72-month visits. Lens refits for the previously untreated T3 cohort were

TABLE 1. Demographics at part 2 baseline for T6 (6 years of treatment) and T3 (original control group refitted with MiSight 1 day for years 4–6)

Variable	T3 group	T6 group	*P*
Subjects (n)	56	52	
Eyes (n)	112	104	
Age entering part 2 (y)			
Mean	13.0	13.2	.60
SD	1.5	1.3	
Range	11 to 15	11 to 16	
Age range, n (%)			
11–12 y	25 (45)	18 (35)	
≥13 y	31 (55)	34 (65)	
Sex, n (%)			
Male	27 (48)	28 (54)	.57
Female	29 (52)	24 (46)	
Ethnicity of subject, n (%)			
White	34 (61)	28 (54)	.94
East Asian	9 (16)	11 (21)	
South Asian	6 (11)	5 (10)	
Other	2 (4)	2 (4)	
Mixed	5 (9)	6 (12)	
Cycloplegic spherical equivalent refractive error (D)			
Mean	–3.45	–2.52	**<.001**
Median	–3.40	–2.50	
SD	1.14	0.98	
Range	–1.31 to –6.88	–0.19 to –4.93	
Axial length (mm)			
Mean	25.07	24.76	**.002**
Median	25.13	24.77	
SD	0.74	0.66	
Range	23.2 to 26.8	23.2 to 27.2	

Values in bold are significant. SD = standard deviation.

appropriately powered for their subjective refraction at 36 months, and acceptable lens fits were confirmed.

The primary outcome measures of cycloplegic spherical equivalent refractive error and cyclopleged optical interferometric measures of axial length were conducted at baseline and annually over the 6-year study using the Grand Seiko Binocular Autorefractor/Keratometer WR-5100 K or WAM-5500 (Grand Seiko Co., Hiroshima, Japan) and the IOLMaster (Carl Zeiss Meditec, Dublin, CA), respectively.

All measurement protocols used in part 1 were retained for part 2.[22] Other additional outcomes collected but not addressed in this article included subject and parent questionnaires, contact lens overrefraction, and lens fit assessment.

Statistical Analysis

The primary effectiveness aims of this study were twofold: (1) to compare myopia progression during part 1 and part 2 for both groups (Hypotheses 1 and 3) and (2) to compare the rate of myopia progression between the two study groups during part 2 and thus evaluate the impact of treatment history (Hypothesis 2).

Demographic data for the T6 and T3 groups were evaluated by the two-sample *t* test (continuous data), Mann-Whitney *U* test (categorical data), or Fisher exact test (nominal data). Unadjusted data for myopia progression are presented as population means with standard deviation. Mixed-effects models—used to analyze the changes in axial length and spherical equivalent refractive error—

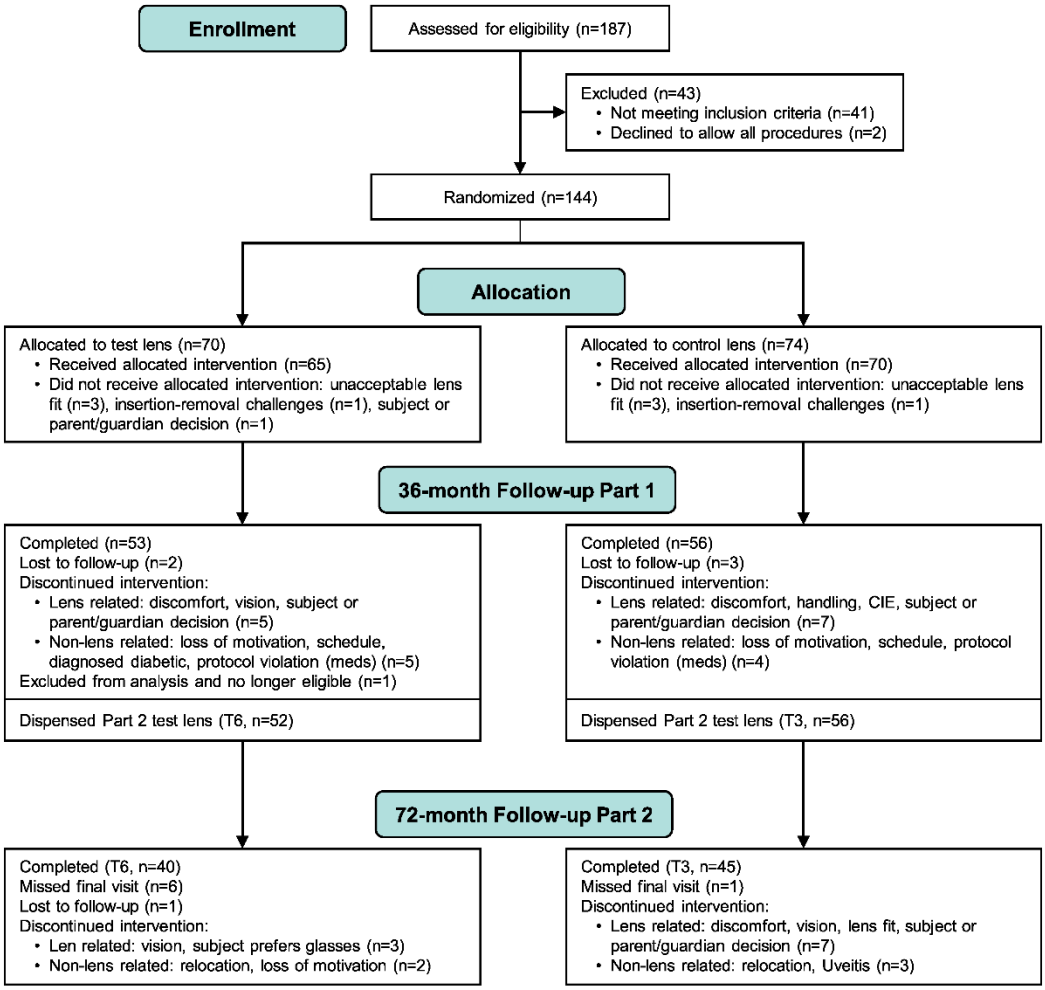


FIGURE 1. Flowchart showing treatment allocations and subject numbers for parts 1 and 2. Discontinuations are detailed as lens related, not lens related, and lost to follow-up.

TABLE 2. Mean spherical equivalent refractive error (in diopters) and axial length (in millimeters) progression with SD for the T6 (6 years of treatment) and T3 (original control then treated in years 4–6) cohorts

Study period	Group	n	Δ Spherical equivalent refractive error, mean ± SD (D)	Δ Axial length, mean ± SD (mm)
Baseline to 36 mo (part 1)	T6	104	−0.51 ± 0.64	+0.30 ± 0.28
	T3	112	−1.24 ± 0.61	+0.62 ± 0.30
36 to 72 mo (part 2)	T6	80	−0.45 ± 0.41	+0.22 ± 0.17
	T3	90	−0.29 ± 0.52	+0.18 ± 0.23
Baseline to 72 mo (parts 1 and 2)	T6	80	−0.92 ± 0.87	+0.49 ± 0.39
	T3	90	−1.55 ± 0.81	+0.81 ± 0.43

Progression during part 1, part 2, and parts 1 and 2 combined is shown. SD = standard deviation.

included group, visit, part, site, and the interactions group by site, group by visit, group by part, and group by visit by part as fixed effects; age at part 1 baseline, part 1 baseline myopia (spherical equivalent refractive error or axial length), and ethnicity were included as fixed covariates; and subject (nested in site) and eye (nested in subject) were included as random effects. The model was used to estimate the mean change from part 1 baseline for each lens group by visit (least squares means and standard error of the mean) and their differences.

The analyses for testing efficacy end points were performed on all evaluable subjects' dispensed lenses at 36 months and subjects who did not have a protocol deviation that was deemed to render data unsuitable for inclusion in the analysis. Safety end points were assessed on all eyes with an evaluable visit, including unscheduled visits, from part 1 dispensing to the 72-month visit.

Comparisons of individual T3 subjects' eye growth rates from part 1 baseline to 36 months with those from 36 to 72 months used Deming regression and cluster analysis (Hypothesis 4).

RESULTS

In part 1 of the study, 144 subjects were enrolled and 135 were dispensed lenses, and 109 subjects completed the 36-month visit.[22] Of these, 108 remained eligible and were dispensed the dual-focus treatment lens for part 2 (52 from the original test group [T6] and 56 from the original control group [T3]). Eighty-five (85) subjects completed part 2 with eligible final visits, 45 in the T3 group and 40 in the T6 group. One subject in the T3 group and six in the T6 group attended a final visit but were not included in the final analysis, as the visits were outside of the allowable visit window.

Table 1 summarizes the demographics for all subjects continuing into part 2. Because most subjects completed part 1, the two cohorts for part 2 continued to be well matched for age, sex, and ethnicity. Owing to differences in their myopia progression during part 1, T3 subjects were, on average, about one diopter more myopic and had longer eyes than T6 subjects at the start of part 2 ($P < .001$ and $P = .002$, respectively).

The age range for subjects entering part 2 of the study was 11 to 16 years, resulting in more than half (60%) of the subjects being older than any subject initiating treatment during part 1 (i.e., 60% were older than 13 years).

Subject Accountability

Fig. 1 shows the flow of participants throughout the clinical trial, from recruitment for part 1 to study completion of part 2.

Of the 108 eligible subjects who consented and were enrolled into part 2, 18 were in Portugal, 23 in the United Kingdom, 18 in Singapore, and 49 in Canada. Ninety-two subjects attended a final 72-month visit. Of these, seven subjects (T6, 6; T3, 1) were 33 or more days late for the 72-month visit (primarily because of scheduling conflicts) and were excluded from the efficacy analysis. Therefore, 85 subjects had eligible final visits, 45 in the T3 group and 40 in the T6 group.

During part 2, 16 subjects discontinued: 6 in the T6 group and 10 in the refitted T3 group. Of those 16 subjects, 7 were discontinued at or soon after the baseline visit (T6, 2; T3, 5). The primary reasons for discontinuing were unacceptable vision (4), preference for spectacles (3), and relocation (3). Overall, the retention rate for those subjects enrolled and dispensed lenses in each part of the study was 81% (109 of 135) for part 1 and 85% (92 of 108) for part 2.

Reported daily hours of wear during weekdays was consistent and high across all 6 years of the study: means ± standard deviations at the 6-month point of part 1 were 12.9 ± 1.3 hours for the T3 group and 12.8 ± 1.2 hours for the T6 group, increasing slightly to 13.9 ± 1.4 and 13.9 ± 1.7 hours for the T3 and T6 groups, respectively, at 72 months. Mean ± standard deviation wearing times reported for weekends were slightly lower at 72 months, 12.9 ± 2.4 and 12.5 ± 1.3 h/d for the T3 and T6 groups, respectively. There were no significant differences

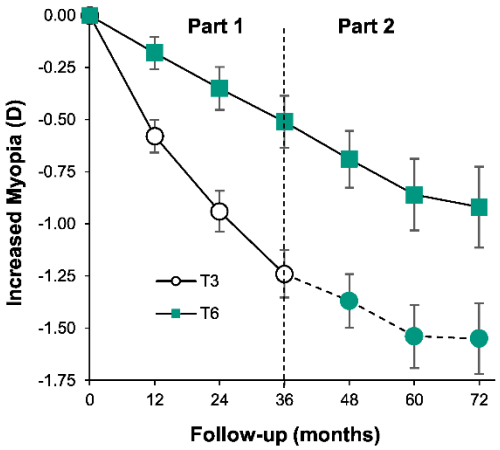


FIGURE 2. Mean change from baseline in cycloplegic spherical equivalent refractive error with 95% confidence intervals. Includes only those subjects enrolled in part 2. Unfilled symbols represent subjects in the control intervention, filled symbols represent subjects in the test intervention.

TABLE 3. Comparison of least squares mean cycloplegic spherical equivalent refractive error progression (in diopters) between part 1 and part 2, and between the T3 and T6 cohorts during part 2

Comparison	Spherical equivalent refractive error, LSM (SEM) (D)	95% CI	Mean difference	95% CI of difference	*P*
T6 group					
Part 1	−0.52 (0.076)	−0.67 to −0.37	0.01 (0.075)	−0.14 to 0.16	.87
Part 2	−0.51 (0.076)	−0.66 to −0.36			
T3 group					
Part 1	−1.32 (0.077)	−1.47 to −1.17	0.98 (0.071)	0.84 to 1.12	<.001
Part 2	−0.34 (0.077)	−0.49 to −0.19			
T6 vs. T3 (part 2)					
T6	−0.51 (0.076)	−0.66 to −0.36	−0.17 (0.094)	−0.35 to 0.02	.08
T3	−0.34 (0.077)	−0.49 to −0.19			

CI = confidence interval; LSM = least squares mean; SEM = standard error of the mean.

between treatment groups for wear time at weekdays or weekends in either part of the study ($P = .19$). However, statistically significantly longer wear times were observed in part 2 compared with part 1 ($P < .001$). During part 2, subjects reported that lenses were worn at least 6.5 d/wk for both lens groups.

Myopia Progression

To quantify change in myopia, differences were calculated between spherical equivalent refractive error, and axial length measured at part 1 baseline and those measured at each annual time point. This normalization process captures the myopia progression during the full study duration (Table 2, Fig. 2). Across the 6 years of assessment, the T3 group (untreated in part 1) progressed by an average of −1.55 ± 0.81 D. This compares with the T6 group who progressed by an average of −0.92 ± 0.87 D. Within the T6 group, 23% of eyes showed no clinically meaningful change in spherical equivalent refractive error (defined as −0.25 D or less) across the full 6 years of treatment.

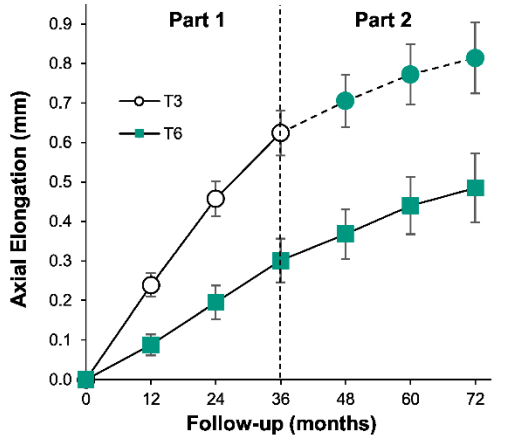


FIGURE 3. Mean change from baseline in axial length with 95% confidence intervals. Includes only those subjects enrolled in part 2. Unfilled symbols represent subjects in the control intervention, filled symbols represent subjects in the test intervention.

The T6 group showed similar spherical equivalent refractive error progression during each of the consecutive 3-year periods, part 1 and part 2, progressing by an average −0.51 ± 0.64 D and −0.45 ± 0.41 D, respectively. During part 2, in which both groups were treated with the dual-focus lens, the T6 and T3 group mean ± standard deviation progression rate was −0.45 ± 0.41 versus −0.29 ± 0.52 D, respectively. The T3 group experienced significant slowing of progression during part 2, slowing from a mean progression of −1.24 D during part 1 to −0.29 D during part 2.

After adjusting for the impact of potential covariables outlined in the statistical analysis plan, the least squares mean estimated progression in spherical equivalent refractive error was calculated. During part 2, no significant difference was observed in progression rate between the two groups at any follow-up visit. Differences in least squares mean refractive progression during part 1 and part 2 were not significant for the T6 group but highly significant for the T3 group (Table 3).

Table 2 and Fig. 3 summarize mean axial length progression for both cohorts. Across the 6 years of assessment, axial lengths in the T3 group increased by an average of 0.81 ± 0.43 mm, whereas axial length in the T6 group increased by an average of 0.49 ± 0.39 mm.

Axial length growth in the T6 group slowed from 0.30 mm in part 1 to 0.22 mm in part 2. This contrasts with the much larger slowing observed in the T3 group as they were switched from control to treatment lenses (0.62 mm in part 1 to 0.18 mm in part 2). During part 2, least squares mean analysis revealed no significant difference in axial length progression between the two groups (Table 4). When comparing axial length growth between parts 1 and 2, the T3 group experienced an average slowing of growth of 0.46 mm ($P < .0001$), whereas the T6 group slowed by only 0.05 mm ($P = .13$; Table 4).

Analysis of Axial Length Changes of Individual Eyes Switched from Control to Test Lenses (T3 Group)

Extending the study for 3 years without a control group did not allow further treatment-versus-control comparison used to establish efficacy in part 1. However, switching the T3 group from a single-vision control lens to a dual-focus treatment lens provided a unique opportunity for longitudinal analysis of eye growth and

TABLE 4. Axial length progression

Comparison	Axial length, LSM (SEM) (mm)	95% CI	Mean difference	95% CI of difference	*P*
T6 group					
Part 1	0.28 (0.033)	0.22–0.34	−0.05 (0.033)	−0.11 to 0.01	.13
Part 2	0.23 (0.033)	0.17–0.30			
T3 group					
Part 1	0.64 (0.033)	0.58–0.71	−0.46 (0.031)	−0.52 to −0.40	<.001
Part 2	0.18 (0.033)	0.12–0.25			
T6 vs. T3 (part 2)					
T6	0.23 (0.033)	0.17–0.30	0.05 (0.040)	−0.03 to 0.13	.25
T3	0.18 (0.033)	0.12–0.25			

Least squares mean estimates and differences comparing progression during part 1 and part 2, and between the T3 and T6 cohorts during part 2. CI = confidence interval; LSM = least squares mean; SEM = standard error of the mean.

myopia development in individual children transitioning from untreated to treated status.

Part 1 and part 2 axial length growth data from the T3 group were used to assess whether a common pattern of slowed eye growth exists in this group of children across the observed range of progression rates in part 1. Specifically, did treatment produce either a fixed amount of slowing[19] for each eye irrespective of the pre-treatment growth or a slowing that scaled with the magnitude

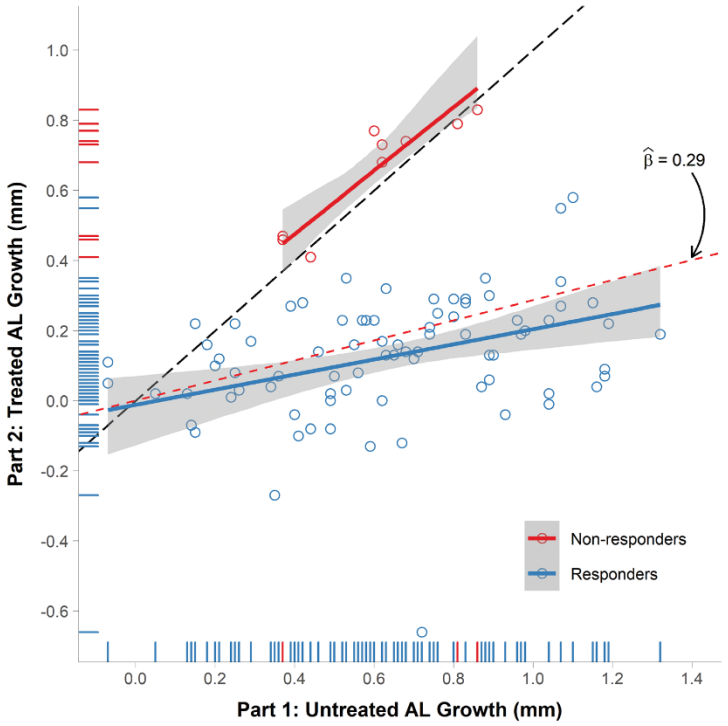


FIGURE 4. Axial length growth of T3 eyes observed over the 3 years of part 2 treatment (*y* axis) compared with growth observed during the part 1 untreated 3-year period (*x* axis). Red dashed line represents the fitted single-parameter model with slope $\hat{\beta}$ = 0.29. Symbols represent individual eyes, blue for the main subgroup (81 eyes) and red for the identified subgroup of "nonresponders" (9 eyes). Solid red and blue lines are best-fit Deming regression lines for each subgroup, gray shaded areas represent a bootstrapped 95% confidence interval on the fitted model, and the black dashed line represents the $Y = X$ values. Red and blue tick marks on the axes reveal the distribution of AL growths during parts 1 and 2. AL = axial length.

of the eye growth seen before treatment (a proportional treatment effect in which eyes that were growing faster before treatment experienced the largest reduction in growth rate)?[29]

Fig. 4 shows a comparison of T3 axial length progression between parts 1 and 2. A Deming regression fit to the full sample of 90 eyes produced an estimated slope of +0.32 and intercept of –0.03, with jackknife 95% confidence intervals (CIs) of 0.06 to 0.59 and –0.19 to 0.14, respectively. A single-parameter model with the intercept set at zero produced a slope of $\hat{\beta}$ +0.29 with 95% CI of 0.21 to 0.37. Importantly, neither fit is consistent with a fixed treatment effect ($Y = X - k$) model. This single-parameter model indicates a 71% slowing of eye growth for the T3 group in part 2.

A subgroup of nine eyes was identified based on statistical criteria for outlier detection and by applying multiple unsupervised learning algorithms to the full N = 90 data set (Fig. 4). Good agreement was found among the best-fitting solutions obtained with two-dimensional kernel density estimation, Gaussian finite mixture modeling, and K-means iterative descent clustering. It is notable that most of these data points (6 of 9) were categorized statistically as "outside" values[30] in the treatment period only; that is, these points were larger than the upper quartile plus 1.5 times the interquartile range. Separate Deming regression of the two subgroups revealed a slope of 0.22 (95% CI, 0.08 to 0.35) and intercept of –0.01 (95% CI, –0.10 to 0.08) for the main group of 81 eyes (90%), with best-fit slopes of 0.90 (95% CI, 0.56 to 1.24) and intercept of 0.11 (95% CI, –0.09 to 0.32) for the nine-eye subgroup. Thus, parameter estimates for the model fitted to the main group data are consistent with a proportional treatment effect ($Y = kX$), whereas the ones from the model fitted to the small subgroup are inconsistent with slowed growth (nonresponding eyes, $Y = X$). Eight of the nine eyes classified as nonresponders were right-left pairs from four subjects. Two eyes of one subject in the main group were significantly shorter after 3 years of treatment (Y values of –0.27 and –0.66 mm). These reduced axial lengths were observed to accumulate annually during the 3 years of treatment. The growth ratios (years 4 to 6/years 1 to 3) were highly correlated for right and left eyes ($R = 0.89$; 95% CI, 0.81 to 0.94).

Additional Outcomes

Visual Acuity

During part 2, mean ± standard deviation distance visual acuities were –0.02 ± 0.07 and –0.03 ± 0.07 logMAR at the dispensing visit for the T3 and T6 groups, respectively. At the final 72-month follow-up, acuities were –0.02 ± 0.08 and –0.02 ± 0.10 respectively, with no significant differences between cohorts across the follow-up visits ($P = .34$).

Rate of Adverse Events and Biomicroscopic Findings

The safety end points—rate of adverse events and biomicroscopic findings >grade 1—have been discussed in detail in a recent publication.[31]

DISCUSSION

Demonstrated efficacy of the dual-focus treatment lens during years 1 to 3 of the 6-year study created ethical and practical reasons to switch from a two-arm randomized control design to one in which all subjects wore the treatment lens for years 4 to 6. This change eliminated the treatment versus control comparisons that were the primary efficacy indicators during part 1 of the study, but it revealed three key results: (1) a sustained rate of slowed eye growth and myopia progression in children who had already experienced 3 years of treatment and (2) a similar rate of myopia progression in a cohort of children introduced to MiSight 1 day contact lenses at an older age, compared with the matched T6 group who had already experienced 3 years of treatment. Eliminating speculation that longer treatment duration will result in a faster progression rate and thus reduced efficacy, compared with a newly treated age-matched population and (3) in the group new to MiSight, significantly reduced myopia progression relative to that experienced during the prior 3-year use of conventional daily disposable contact lenses.

For the originally treated cohort (T6), there was little difference between the least squares mean myopia progression for part 1 and part 2 (mean difference, 0.01 D and 0.05 mm). This suggests that the myopia control treatment with dual-focus contact lenses shows a sustained slowed eye growth over time and supports the value of a prolonged treatment through childhood and into adolescence. However, this sustained slowed eye growth may not directly translate to efficacy, given that older age can also result in slower eye growth in untreated eyes. During part 2, the group new to MiSight 1 day (T3) experienced slightly slower progression (not statistically different) to that observed in the demographically matched T6 group, suggesting that treatment efficacy is not significantly affected by prior treatment. Also, this similar progression of the T3 group occurred despite their generally higher myopia levels and longer eyes after an absence of treatment in part 1.

Average spherical equivalent refractive error progression of the T3 cohort was slowed by nearly a diopter (0.98 D) in part 2, and axial length growth was reduced by 0.46 mm. This significant slowing of eye growth was observed in all but nine of the eyes newly treated with MiSight 1 day in part 2 who were older (age, 13 to 15 years) than the age range of subjects enrolled into part 1 (8 to 12 years). Overall, these results provided evidence of treatment efficacy in children who were, on average, 3 years older than those recruited into the original treated cohort.

The within-eye comparisons of growth during and before treatment of the T3 cohort (Fig. 4) are consistent with a proportional effect for myopia control across the progression range and revealed growth rates during part 2 that were, on average, 29% of the rate observed during part 1. The 29% result cannot be interpreted as a 71% treatment effect because increasing age in itself would account for some slowing of growth during part 2. Analysis using published eye growth models[10] shows that, if left untreated, axial length growth for untreated myopes in the older age range would, on average, be approximately 76% of that observed in the 3-year-younger, original control group enrolled in part 1. In other words, approximately one-third of the slowing of eye growth observed during part 2 can be attributed to age.

Comparisons of axial length growth between parts 1 and 2 of the T3 cohort also provided the opportunity to identify any potential "nonresponders," an advantage provided by switching the T3 group, whose myopia progression before treatment had been well defined, into treatment lenses. Nonresponders could not be identified in part 1 because faster progressors in the treatment group may have progressed more than average because they did not respond to treatment or because they did respond to treatment, but their growth rate, if left untreated, would have been even faster. Applying statistical outlier detection to the data identified 10% (9

of 90) of eyes as belonging to the subgroup for whom the treatment lens did not slow eye growth.

Although Deming regression analysis (Fig. 4) of the majority subgroup reveals that growth during treatment was, on average, 22% of that before treatment, many subjects experienced approximately zero growth during treatment, whereas others grew at up to 30 to 50% of the pre-treatment rate. Although the data support a proportional treatment model over a model in which treatment slows growth in all children to a low level that is independent of their pre-treatment growth, the CI for a Deming regression of the "responder" subgroup overlaps with that of $Y =$ constant model over a significant range of values of untreated axial length growth. The data do not support a fixed treatment effect where slowed progression is fixed number of millimeters regardless of part 1 progression rate.

Finally, it should be noted that this study represents one of the longest prospective interventional trials of pediatric soft contact lens wear. As such, the clinical and, in particular, safety end points are worthy of note. The previously reported low rate of significant biomicroscopic findings[31] further illustrates the minimal impact on ocular physiology in this younger population with full-time, daily disposable contact lens wear and is an important finding for eye care professionals considering recommending contact lens myopia control for children.

In conclusion, these 6-year data provide compelling evidence of an accumulating myopia control effect of a dual-focus contact lens as treatment duration is extended and beneficial effects even when treatment is commenced at an older age. The data for the refit T3 cohort are consistent with the hypothesis that treatment effect is proportional to pre-treatment growth rates and thus larger for fast-growing eyes. As such, this result emphasizes the added value of treatment to the fast progressors, who are at the greatest future risk of maculopathy.[4]

ARTICLE INFORMATION

Submitted: August 18, 2021

Accepted: December 30, 2021

Funding/Support: CooperVision Inc. (to PC). The study was sponsored by CooperVision Inc. No additional funding was received by the investigator or contract research organization.

Conflict of Interest Disclosure: PC, AB, BA, DH, and JM are employees of the sponsor. The sponsor participated in study design, analysis, and interpretation. The authors were responsible for the preparation of this article and the decision to submit this article for publication. The contract research organization had full access to the study data; the investigators had partial access to the study data and take full responsibility for their presentation in this article. The lead author affirms that the article is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. All investigators were independent from the study sponsor and take responsibility for the integrity of the data. All additional authors have critically reviewed the article for important intellectual content.

Study Registration Information: This study is registered on ClinicalTrials.gov (identifier NCT01729208).

Author Contributions and Acknowledgments: Conceptualization: PC, JM, GY; Data Curation: CH; Formal Analysis: PC, AB, BA, DH, JM, CH, GY; Investigation: NSL, DJ, CN, SCP-d-M; Project Administration: PC, JM, GY; Validation: CH; Writing – Original Draft: PC, AB; Writing – Review & Editing: PC, AB, BA, DH, JM, NSL, DJ, CN, SCP-d-M, CH, GY.

The clinical trial reported in this article was sponsored by CooperVision, Inc.

Martin Rickert, PhD, provided statistical consulting services.

MiSight 1 day Clinical Study Group

Visioncare Research Limited, Farnham, Surrey, United Kingdom

Graeme Young (Medical Monitor), Chris Hunt (Statistician), Ruth Craven (Clinical Research Manager), Susanna Jones (Project Manager), Michael Spyridon, Tom Boyes, Sarah McCready, Kristina Roslin (Clinical Research Associates), Shaun Peters (Clinical Research Coordinator), Tricia Riley, Emma Lyle, Glenis Rogers (Data Entry).

University of Minho, CEOR Lab

José Manuel González-Méijome (Principal Investigator), Sofia Cláudia Peixoto-de-Matos, Ana Maria Fernandes de Pinho Dias, Helena Isabel Ferreira-Neves, Daniela Patricia Lopes-Ferreira, Ana Amorim-de-Sousa (Coinvestigators).

Aston University, School of Optometry

Nicola Logan (Principal Investigator), Susie Jones, Fi Cruickshank (Coinvestigators).

National University Health System, Ophthalmology Department, Singapore

Seang Mei Saw (Chief Investigator), Cheryl Ngo (Principal Investigator, 2014–current; Coinvestigator, 2012–2014), Inez By Wong (Principal Investigator, 2012–2014), Ivy Law (Administrative Manager), Ray Manotosh, Michelle Lim, Amanda Lim (Coinvestigators), Anny Leow (Coordinator).

University of Waterloo School of Optometry, Waterloo, Canada

Lyndon Jones (Principal Investigator), Debbie Jones (Lead Investigator), Jill Woods, Mike Yang, Karen Walsh (Coinvestigators), Jane Johnson (Clinical Assistant).

REFERENCES

1. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016;123:1036–42.

2. Flitcroft DI, He M, Jonas JB, et al. IMI—Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. Invest Ophthalmol Vis Sci 2019;60:M20–30.

3. Tideman JW, Snabel MC, Tedja MS, et al. Association of Axial Length with Risk of Uncorrectable Visual Impairment for Europeans with Myopia. JAMA Ophthalmol 2016;134:1355–63.

4. Flitcroft DI. The Complex Interactions of Retinal, Optical and Environmental Factors in Myopia Aetiology. Prog Retin Eye Res 2012;31:622–60.

5. Klaver CC, Wolfs RC, Vingerling JR, et al. Age-specific Prevalence and Causes of Blindness and Visual Impairment in an Older Population: The Rotterdam Study. Arch Ophthalmol 1998;116:653–8.

6. Tang Y, Wang X, Wang J, et al. Prevalence and Causes of Visual Impairment in a Chinese Adult Population: The Taizhou Eye Study. Ophthalmology 2015;122:1480–8.

7. Xiao O, Guo X, Wang D, et al. Distribution and Severity of Myopic Maculopathy among Highly Myopic Eyes. Invest Ophthalmol Vis Sci 2018;59:4880–5.

8. Chua SY, Ikram MK, Tan CS, et al. Relative Contribution of Risk Factors for Early-onset Myopia in Young Asian Children. Invest Ophthalmol Vis Sci 2015;56:8101–7.

9. COMET Group. Myopia Stabilization and Associated Factors among Participants in the Correction of Myopia Evaluation Trial (COMET). Invest Ophthalmol Vis Sci 2013;54:7871–84.

10. Jones LA, Mitchell GL, Mutti DO, et al. Comparison of Ocular Component Growth Curves among Refractive Error Groups in Children. Invest Ophthalmol Vis Sci 2005;46:2317–27.

11. Tideman JL, Polling JR, Vingerling JR, et al. Axial Length Growth and the Risk of Developing Myopia in European Children. Acta Ophthalmol 2018;96:301–9.

12. Chua SY, Sabanayagam C, Cheung YB, et al. Age of Onset of Myopia Predicts Risk of High Myopia in Later Childhood in Myopic Singapore Children. Ophthalmic Physiol Opt 2016;36:388–94.

13. Zhou Z, Chen T, Wang M, et al. Pilot Study of a Novel Classroom Designed to Prevent Myopia by Increasing Children's Exposure to Outdoor Light. PLoS One 2017;12:e0181772.

14. Wu PC, Chen CT, Lin KK, et al. Myopia Prevention and Outdoor Light Intensity in a School-based Cluster Randomized Trial. Ophthalmology 2018;125:1239–50.

15. He M, Xiang F, Zeng Y, et al. Effect of Time Spent Outdoors at School on the Development of Myopia among Children in China: A Randomized Clinical Trial. JAMA 2015;314:1142–8.

16. Xiong S, Sankaridurg P, Naduvilath T, et al. Time Spent in Outdoor Activities in Relation to Myopia Prevention and Control: A Meta-analysis and Systematic Review. Acta Ophthalmol 2017;95:551–66.

17. Walline JJ, Lindsley KB, Vedula SS, et al. Interventions to Slow Progression of Myopia in Children. Cochrane Database Syst Rev 2020;1:CD004916.

18. Mutti DO, Hayes JR, Mitchell GL, et al. Refractive Error, Axial Length, and Relative Peripheral Refractive Error Before and After the Onset of Myopia. Invest Ophthalmol Vis Sci 2007;48:2510–9.

19. Brennan NA, Toubouti YM, Cheng X, et al. Efficacy in Myopia Control. Prog Retin Eye Res 2021;83:100923.

20. Ashcroft R. Equipoise, Knowledge and Ethics in Clinical Research and Practice. Hum Exp Res 2017;13:433–45.

21. Gupta U, Verma M. Placebo in Clinical Trials. Perspect Clin Res 2013;4:49–52.

22. Chamberlain P, Peixoto-de-Matos SC, Logan NS, et al. A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control. Optom Vis Sci 2019;96:556–67.

23. Cheng D, Woo GC, Drobe B, et al. Effect of Bifocal and Prismatic Bifocal Spectacles on Myopia Progression in Children: Three-year Results of a Randomized Clinical Trial. JAMA Ophthalmol 2014;132:258–64.

24. Gwiazda J, Hyman L, Hussein M, et al. A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children. Invest Ophthalmol Vis Sci 2003;44:1492–500.

25. Walline JJ, Walker MK, Mutti DO, et al. Effect of High Add Power, Medium Add Power, or Single-vision Contact Lenses on Myopia Progression in Children: The Blink Randomized Clinical Trial. JAMA 2020; 324:571–80.

26. U.S. Food and Drug Administration (FDA), Pre-market Arroval: Medical Devices. MiSight 1 Day (Omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P180035. Accessed October 29, 2021.

27. Evans SR. Clinical Trial Structures. J Exp Stroke Transl Med 2010;3:8–18.

28. Bassler D, Montori VM, Briel M, et al. Early Stopping of Randomized Clinical Trials for Overt Efficacy Is Problematic. J Clin Epidemiol 2008;61: 241–6.

29. Anstice NS, Phillips JR. Effect of Dual-focus Soft Contact Lens Wear on Axial Myopia Progression in Children. Ophthalmology 2011;118:1152–61.

30. Tukey JW. Exploratory Data Analysis. Reading, MA: Addison Wesley Pub. Co.; 1977.

31. Woods J, Jones D, Jones L, et al. Ocular Health of Children Wearing Daily Disposable Contact Lenses over a 6-year Period. Cont Lens Anterior Eye 2021; 44:101391.

CHAPTER 5: OCULAR HEALTH AND SAFETY IN A LONGITUDINAL TRIAL OF SOFT CONTACT LENSES

5.1. Application of contact lens aftercare principles to MiSight trial

The concept and application of aftercare play a critical role in healthcare, particularly when prescribing a medical device. This becomes even more crucial when the recipient is a pediatric patient, where ongoing monitoring is essential to ensure both safety and efficacy. In optometry, conditions such as myopia and presbyopia are progressive, requiring frequent follow-ups to maintain optimal vision correction.

In the case of contact lens aftercare, regular monitoring serves as a protective measure against potential adverse ocular responses. Since contact lenses interact directly with the exposed epithelium and may disrupt normal corneal physiology, aftercare is critical in detecting early complications. (Efron 2019) Close monitoring during the adaptation phase allows clinicians to detect early signs of chronic responses to contact lens wear or issues with lens fitting, preventing long-term complications.

A review by Efron and Morgan examined the historical and clinical perspectives of contact lens aftercare. (Efron and Morgan 2017) They identified four key motivations for follow-up visits:

1. Preserving ocular health
2. Maintaining good vision
3. Optimizing comfort
4. Ensuring proper lens fit and performance.

Among these factors, preserving ocular health was of paramount importance when designing the clinical trial for this myopia control intervention. At the time of study design, longitudinal data on soft contact lens wear in children was limited. Additionally, the study specifically aimed to recruit children with no prior experience in soft contact lens wear, further emphasizing the need for careful aftercare protocols to ensure safe adaptation and sustained ocular health throughout the trial.

Complications related to the wearing of soft contact lenses in the general population are relatively common. (Efron and Morgan 2017) Approximately one third of wearers have reported experiencing some sort of complication from contact lens wear. (Donshik, Ehlers et al. 2007, Cope, Collier et al. 2015) Complications in turn may result in a temporary abandonment of lens wear, reduction in wear time, or more seriously loss in vision. Adverse events are generally classed into two broad categories; Serious – a category that includes microbial keratitis, a condition associated with soft contact lens wear, which can result in a permanent change to a body structure (i.e. the cornea) and in some cases loss of vision; and Non–Serious – this category includes all other adverse events that are not vision threatening and do not result in a permanent change in body structure. Non-serious events are further classified into significant and non-significant. Significant events are usually symptomatic and likely result in a temporary cessation of lens wear, but do not threaten long term vision or ocular health. They often require some sort of treatment intervention that likely includes temporary cessation of contact lens wear. Examples of significant adverse events include a Contact Lens Induced Peripheral Ulcer (CLPU), a non-infectious corneal inflammatory event. Non-significant events are often asymptomatic and do not result in permanent damage to a structure but may require temporary cessation of lens wear, perhaps to guard against sequential problems. Events in this category include ocular conditions unrelated to contact lens wear like blepharitis and conjunctivitis. Routine aftercare appointments, as reflected in the visit schedule for this research trial, are appropriate to observe chronic asymptomatic or mildly symptomatic complications of soft contact lens wear that would not trigger an unscheduled visit to the eye-care practitioner.

Table 1 (Adapted from Stapleton et al 2021) provides a list of complications and adverse events associated with soft contact lenses that are most relevant to modern disposable hydrogel and silicone hydrogel materials. (Stapleton, Bakkar et al. 2021)

Category	Condition	Acute / Chronic
Infection	Microbial Keratitis	Acute
Inflammation	Infiltrative keratitis	Acute
Metabolic/ Hypoxic	Epithelial Oedema	Chronic
	Microcysts	Chronic
	Vacuoles	Chronic
	Stromal oedema	Chronic
	Stromal vascularization	Chronic
	Endothelial blebs	Chronic
	Endothelial Polymegathism / Polymorphism	Chronic
Mechanical	Corneal abrasion / erosion	Acute
	Superior epithelial arcuate lesion (SEAL)	Acute
	Contact lens related papillary conjunctivitis (CLPC)	Chronic
	Lid Wiper Epitheliopathy	Chronic
Toxic/Allergic	Contact lens related papillary conjunctivitis (CLPC)	Chronic
	Solution Induced Corneal Staining (SICS)	Acute/Chronic
Dry eye	Meibomian Gland Dysfunction (MGD)	Chronic
	Conjunctival Staining	Chronic
	Corneal staining	Chronic

Table 1: Examples of contact lens associated complication.

The rapid pace of development in the soft contact lens industry over the last 30 years has contributed to some of the listed complications being less commonly observed. When the need for frequent contact lens aftercare was first established, it was partially in response to chronic conditions more commonly observed in low water content, low oxygen transmissibility materials with extended replacement cycles. The advent of first high water content hydrogel materials (Lippman 1990) and then silicon hydrogel materials (Alvord, Court et al. 1998, Morgan and Efron 2002) eliminated some of these chronic conditions. Further, the advent of disposable lenses, beginning with monthly and progressing to daily disposable lenses in 1994 also contributed to fewer contact lens complications being observed at routine follow up appointments. (Efron 2018, Tanner and Efron 2018, Efron 2024) Daily disposable lenses eliminated the need for chemical disinfection systems and appear to have reduced the severity of many contact lens complications. (Dart, Radford et al. 2008, Stapleton, Keay et al. 2008)

Despite significant advancements in the field of contact lenses, concerns persist, particularly regarding the prescription of soft contact lenses for children. A recent update to a global survey on attitudes toward myopia control, conducted by Wolffsohn et al., highlighted safety concerns as a primary reason for hesitancy in prescribing myopia control interventions. (Wolffsohn, Calossi et al. 2016, Wolffsohn, Calossi et al. 2020) The largest proportion of respondents—one-third of surveyed practitioners—cited 'inadequate information' as the main factor behind their reluctance to recommend myopia control contact lenses for children.

In the United States, prescribing data estimated that pediatric contact lens fittings (for individuals under 18) account for approximately 11% of all contact lens fits. (Efron, Nichols et al. 2015) A similar global survey applying the same methodology revealed that soft contact lens fittings for children aged 6-12—an age range closely mirroring the baseline ages of subjects in the MiSight trial (8-12 years)—represented only 1.6% of all contact lens fits.

(Efron, Morgan et al. 2011) However, the introduction of myopia control soft contact lenses has led to a gradual increase in their use among children and adolescents, with utilization rising to approximately 7% of all lens fits by 2018. (Efron, Morgan et al. 2020)

Further insights from a U.S.-based optometrist survey indicate that practitioners generally recommend initiating contact lens wear between the ages of 10 to 12. (Sindt and Riley 2011) However, these findings may be subject to response bias, as optometrists willing to participate in surveys about pediatric contact lens fitting may not be fully representative of the profession as a whole.

In summary these data emphasize a need for greater information about safety of soft contact lenses in children. Do children's eyes respond similarly to those of adult contact lens wearers? Therefore, the clinical trial designed to quantify the efficacy of myopia control contact lenses in children offered the opportunity to explore the ocular health consequences of daily contact lens wear in a pediatric population.

The MiSight study monitored the impact of full-time soft contact lens wear on chronic or acute complications in a young population. The methods used for grading and tracking of contact lens complications such as those identified in Table 1 is well established. Terry et al, proposed a set of standards for establishing criteria for clinically acceptable changes in anterior ocular health during contact lens wear. (Terry, Schnider et al. 1993) The CCLRU grading system, whilst modified over time, has provided the foundation for assessing the ocular response to contact lens wear over the last 30 years, and was employed in the current trial.

Limbal hyperemia, is commonly associated with contact lens wear, and has shown to be correlated to the oxygen transmissibility of the contact lens material. (Papas, Vajdic et al. 1997) Limbal vessels are located at the corneal periphery, in close proximity to limbal epithelial stem cells, which are essential for the regeneration of the corneal epithelium. Hypoxic conditions in this region can adversely affect the function and renewal of these stem cells. Studies have shown that hypoxia can disrupt the microenvironment of the limbus, leading to compromised stem cell activity and potential corneal surface abnormalities. (Wang, González et al. 2016) These changes, if chronic can progress to corneal vascularization which is present more often in contact lens wearers than with non-lens wearers. (Holden, Sweeney et al. 1986) In severe cases, proliferation of immature new vessels can lead to other complications, potentially resulting in loss of acuity. (Efron 2019)

These chronic complications related to hypoxia are potentially of particular concern for the design of this protocol. As mentioned, the material of the MiSight 1 day lens is hydrogel, which with a reported Dk (oxygen transmissibility) of 25 x 1011, a transmissibility level approximately 4-5 times lower than many of the modern silicon hydrogel materials. The clinical protocol also required full time wear of a minimum 6 days per week and 10 hours per day, to reduce the likelihood of lack of wear time becoming a confounding factor in the myopia progression result.

Epithelial cell disruptions leading to corneal staining can occur as either an acute or chronic consequence of contact lens wear. Detection of epithelial damage is performed using sodium fluorescein, a dye that penetrates compromised cell membranes or gaps between damaged epithelial cells. The standard application method involves moistening sodium fluorescein strips with sterile saline before placing them in the inferior conjunctival sac. This staining technique allows clinicians to assess corneal integrity, as areas of disrupted epithelium take up fluorescein and become visible under blue light. (Terry, Schnider et al. 1993) The presence of corneal staining, or more specifically a break in the protective epithelial barrier, may increase susceptibility to infection. (Vaidyanathan, Hopping et al. 2019) Corneal staining is graded based on size, extent, and location (superior, inferior, temporal, nasal, or central), facilitating diagnosis of underlying causes. As detailed in Table 1, toxic (lens care solution-related), mechanical, dehydration-induced, or infectious insults can result in staining.

Contact lens-induced papillary conjunctivitis (CLPC) is a chronic inflammatory condition that commonly occurs with contact lens wear due to repeated mechanical irritation of the palpebral conjunctiva during blinking. Clinically, the conjunctiva exhibits increased redness and rough papillary formations ("papillae"). Without intervention, the condition may progress to giant papillary conjunctivitis (GPC), characterized by enlarged papillae (>1mm). Both conditions may lead to excess mucus production, blurred vision, itching, and reduced tolerance to contact lens wear.

Corneal infiltrative events (CIEs) include infiltrative keratitis (IK) and contact lens peripheral ulcer (CLPU). IK typically presents with mild or no symptoms, slight redness, and small, multiple infiltrates, whereas CLPU appears as a distinct corneal lesion in the periphery, visible due to fluorescein staining, indicating epithelial disruption. Unlike infectious corneal ulcers, CLPUs typically exhibit well-defined borders, allowing differentiation. While CIEs are generally considered non-infectious, some researchers (Morgan & Efron) have proposed that they may exist on a continuum with infectious keratitis, meaning that some cases may represent early-stage microbial infections. (Morgan, Efron et al. 2005, Efron and Morgan 2006) This hypothesis has clinical merit, as many clinicians adopt a precautionary approach by treating severe CIEs as potential infectious keratitis. However, this continuum model complicates efforts to precisely classify and estimate the incidence of corneal infiltrative complications of specific severities.

The incidence of corneal infiltrates appears to be between 2-3% per year with continuous wear of silicone hydrogel lenses, and the additional factor of the closed eye wear during sleep can add an additional risk. (Chalmers, McNally et al. 2007) Similar rates are estimated in daily wear silicone hydrogel. Daily disposable hydrogel lenses like MiSight 1 day pose less risk (between 0 and 0.14% per year). (Chalmers, Hickson-Curran et al. 2015) There is little available data to explore the covariate of patient age on the incidence of CIE with contact lens wear. However, the “Contact Lens Assessment in Youth (CLAY)” study provides some insight. (Lam, Kinoshita et al. 2011) This study was a multicenter retrospective study targeted to assess the safety of soft contact lenses in this population via events that interrupted lens wear within eye care clinics in a university setting. Additional measures outside of the controlled environment of a clinical trial were collected on young wearers from age 8 to 34 years of age. The results showed that age was a significant nonlinear factor in the incidence of CIE, with the lowest incidence occurring in the 8-12 year olds and the highest in the 18-25 age group. (Chalmers, Wagner et al. 2011) In a subsequent analysis from the same study, Wagner et al surveyed risk factors and found a correlation between the ages with greater events and the propensity for less compliant behaviors in contact lens wear. (Wagner, Chalmers et al. 2011) Whilst not a clear causal relationship, the data highlight the benefits of clear instructions to patients and the use of aftercare visits to reinforce those practices. Overall, the incidence of CIE in this study were between 3-4% per year of wear in this real-world setting, with the incidence in the younger population lying somewhere between 0.3 - 2.3% per year. When considering risk factors for the occurrence of CIE overnight wear, reusable lenses with multi-purpose cleaning solution (versus hydrogen peroxide) and, perhaps surprisingly, use of silicone hydrogel lenses were the key modifiable risk factors contributing to a greater odd of suffering a CIE event. The same analysis found the 1st year of wear as a non-modifiable risk factor. (Chalmers, Wagner et al. 2011)

In summary, as proposed in a recent review paper by Bullimore, this literature fails to find evidence that corneal infiltrative events associated with contact lens wear is greater in younger populations than in adults, and may in fact be lower in the 8-11 age group. (Bullimore 2017) However, given the proposed specific indication of use for the MiSight lens, with the expectation of 6 days per week of >10 hours wear, careful monitoring of corneal health in the young subjects (ages 8-12 at baseline) was warranted.

The most concerning potential complication of contact lens wear to most eye care practitioners is microbial keratitis. Despite being a rare complication, the potential loss of

vision is a significant personal and societal cost. As discussed earlier in the chapter, regardless of whether the condition is part of a CIE continuum, (Efron and Morgan 2006) failure to conduct early assessment and treatment can lead to more severe consequences. (Keay, Edwards et al. 2006) Microbial Keratitis risk factors include overnight wear, with the risk increasing the longer overnight wear is prescribed especially when using hydrogel lenses. Smoking was another modifiable risk factor associated with increased odds of infection. Lower socio-economic class was a non-modifiable risk factor but being female gender was protective. (Keay, Stapleton et al. 2007) A daily disposable contact lens wearing modality, such as that employed in the MiSight trial, has been speculated to result in lower severity of the condition. (Stapleton, Bakkar et al. 2021)

A clear definition of a condition is critical in both clinical practice and epidemiological studies. The most common definition of microbial keratitis for the purposes of diagnosis specifies: One or more corneal stromal infiltrates greater than 1 mm with pain mild plus 1 or more of either anterior chamber reaction greater than minimal or mucopurulent discharge or positive corneal culture. This same definition was applied in the analysis reviewed in the following publications within this chapter. Early reports of the incidence of microbial keratitis in daily wear indicate between 2.5 and 5 (Poggio, Glynn et al. 1989, Cheng, Leung et al. 1999) or approximately 2 per 10000. (Stapleton, Keay et al. 2008) The lower incidence levels observed in the more recent study may be attributable to methodological differences between the epidemiological studies or possibly enhancement in contact lens material or care solution. The latter study also assessed the rate for overnight wear to be 20 per 10000 in overnight wear, which is supported by a FDA mandated post market surveillance study on the lotrafilcon A material. (Schein, McNally et al. 2005)

There are no formal epidemiological studies exploring the rate of microbial keratitis (MK) in children. However, Bullimore in a review paper examined a number of long-term studies which reported safety outcomes including MK. (Bullimore 2017) The review found none of the prospective studies reported MK. The CLAY study found evidence of 2 cases in the 13-17 age group, but none in the 8-12 age group. Despite this encouraging picture in a younger age group, there was a clear absence of data in this age group. Concern over this gap in the literature was repeatedly raised during preliminary discussions with regulatory bodies when seeking clearance of the MiSight clinical trial. To supplement the prospective monitoring of eyes enrolled in the MiSight efficacy study, we planned a retrospective chart review as a novel method to ascertain a rate of MK in contact lens wearing children. This study assessed the MK rate in general contact lens wear, versus in our efficacy trial, which had insufficient power to establish a rate of this rare condition.

The following publications explore first the presence of contact lens complications in the MiSight trial and the rate of microbial keratitis in young contact lens wearers, matched in age to those enrolling in the MiSight trial, but in a real-world setting.

5.2. Publication: Ocular health of children wearing daily disposable contact lenses over a 6-year period

Contact Lens and Anterior Eye 44 (2021) 101391

Contents lists available at ScienceDirect

Contact Lens and Anterior Eye

journal homepage: www.elsevier.com/locate/clae

Ocular health of children wearing daily disposable contact lenses over a 6-year period

Jill Woods [a,*], Debbie Jones [a,b], Lyndon Jones [a,b], Susanna Jones [c], Chris Hunt [c], Paul Chamberlain [d], John McNally [d]

[a] Centre for Ocular Research & Education (CORE), School of Optometry & Vision Science, University of Waterloo, 200 University Ave W, Waterloo, ON N2L 3G1, Canada
[b] Centre for Eye & Vision Research, Hong Kong
[c] Visioncare Research Ltd., Craven House, West Street, Farnham, Surrey, GU9 7EN, UK
[d] CooperVision, Inc., 6150 Stoneridge Mall Rd, Pleasanton, CA 94588, United States

ARTICLE INFO

Keywords:
Neophyte
Children
Soft contact lenses
Safety profile
Adverse events
MiSight

ABSTRACT

Purpose: To report on the ocular health and safety of children fit with soft hydrogel daily-disposable contact lenses, and followed for 6-years in a double-masked clinical trial investigating the performance of a dual-focus contact lens designed to control myopia progression.
Methods: Children aged 8–12 years, naïve to contact lens wear, were enrolled across four international sites. During years 1–3, children were randomised to either MiSight® 1 day or Proclear® 1 day (both omafilcon A, CooperVision, Inc.). The lenses were identical in material and geometry except for the front optical zone design. At the end of year-3, all those wearing Proclear 1 day were switched to MiSight 1 day, therefore all wore MiSight 1 day in years 4 6. Subjects agreed to wear the lenses at least 10-hours/day, 6-days/week. After dispensing, study visits were at 1-week, 1-month, 6-months and every 6-months until 6-years. At each visit, ocular measurements and subjective responses were recorded. Biomicroscopy used 0–4 grading scales; grade 0 represented no findings.
Results: 144 children were enrolled: 69F:75M; mean age 10.1 years; mean cycloplegic spherical-equivalent refraction -2.11D; ethnicities included 34 East-Asian, 12 West-Asian, and 79 Caucasian. 92 completed the 6-years. Only three subjects discontinued due to an ocular adverse event (AE). No contact lens related AEs were classified as serious. The incidence rate of infiltrative AEs was 0.61% (6.1/1000 wearing-years; 95%CI: 0.24%–1.57%). The most common biomicroscopy findings were limbal, bulbar and tarsal hyperaemia and tarsal roughness. 99% of all biomicroscopy findings were grade-1 or lower. After 6-years of lens wear, ocular health by biomicroscopy was similar to pre-lens wear.
Conclusions: Across the 6-years, there were no contact lens related serious AEs and biomicroscopy showed no significant changes. Results suggest that children this age can successfully wear daily-disposable hydrogel contact lenses with minimal impact on ocular physiology.

1. Introduction

Fitting children with soft contact lenses for myopia control currently represents a very small percentage of all soft lens fits. [1] However, interest in this category is increasing worldwide, with many reports supporting soft lenses as a viable option for children and for myopia progression control specifically [2–10].

The average age of first contact lens fit can be expected to decrease as both parents and practitioners show increased interest in the benefits of myopia control lens designs. About a decade ago, initial contact lens fits for refractive correction were typically only undertaken on teenagers. [11,12] A recent fitting survey report indicates that the current median age for myopia control soft lens fitting is age 12, and that fitting children as young as age 8 is increasing in frequency [13]. With the increasing prevalence of myopia globally, particularly in Asia [14], it is anticipated that fitting children as young as age 8 will become more commonplace. The safety of soft contact lens wear for children in this age group requires evaluation. Areas of consideration are inflammatory/infection

* Corresponding author.
E-mail address: jwoods@uwaterloo.ca (J. Woods).

https://doi.org/10.1016/j.clae.2020.11.011
Received 30 July 2020; Received in revised form 29 October 2020; Accepted 22 November 2020
Available online 4 February 2021

risk as well as contact lens induced mechanical or hypoxic responses.

Many publications have addressed the risk factors for ocular adverse responses in soft lens wearers, both for an adult population, [15–23] as well as in child and teenage populations [11,24–30]. A consistent message from many such reports is that the risk of adverse responses is lower with a daily disposable modality compared to re-usable daily wear lenses [22,23,26,29,31]. Despite this wealth of literature, there are very few multi-year prospective investigations that report specifically on the physiological response to daily disposable soft contact lens wear in young children and adolescents [28,32,33]. Prior to this paper, the longest such physiological report in the literature specific to children wearing a daily disposable soft lens is a 3-year clinical trial published by Walline et al. [32]

When children are fit with contact lenses for myopia control, it is anticipated that they will wear lenses for decades. Lenses will be worn at least throughout their adolescent years while the risk of myopia progression remains, and quite likely throughout adult life as a refractive error correction. Providing practitioners with data about adverse events and the ocular physiological response of children to contact lens wear will allow them to better counsel patients, and their parents, on the risks and benefits of soft lenses as an option for myopia control. For this reason, multi-year prospective data from clinical trials with frequent follow-up and careful examination will serve to further inform the profession. This paper presents physiological response data from a long-term clinical trial, observing children fit with daily disposable soft contact lenses and followed through early adolescence.

2. Methods

The clinical trial was designed to compare the clinical performance of a dual-focus daily disposable contact lens designed to slow myopia progression (MiSight® 1 day, CooperVision, Inc.) to a marketed daily disposable contact lens (Proclear® 1 day, CooperVision, Inc.). The study was conducted at four sites in four countries; Canada, Portugal, Singapore and the United Kingdom. All study investigators were trained on the ICH guidelines for Good Clinical Practice and the study was conducted in accordance with the tenets of the 1964 Helsinki Declaration and its later amendments.

During the first three years, the study design was a randomised, double masked (child, parent and investigator) parallel group clinical trial. After meeting eligibility requirements, children were randomised to wear either MiSight 1 day or Proclear 1 day. Details of the clinical trial design and the results regarding myopia control effectiveness over three years have been presented in an earlier publication. [8] At the 3-year visit, all children were offered the possibility of continuing in the second phase of the study, in which they would be dispensed with open-label MiSight 1 day lenses and followed for an additional three years.

Both study lenses were the omafilcon A material and were identical in diameter, base curve design, edge design and overall thickness and geometry (Table 1). The only difference between the lenses was the inclusion of the front surface dual-focus centre-distance optical zone in the MiSight 1 day lens, which is designed to slow the progression of myopia in children. This front surface curvature design difference has negligible impact on lens thickness or surface smoothness. Based on these similarities, both lenses could be assumed to be equivalent from the perspective of mechanical or physiological interaction with the ocular surfaces. Thus, data from the two lens types are combined for the purposes of reporting physiological response and adverse events in this population of children followed for six years.

Table 1
Contact lens parameters used in the clinical trial.

	MiSight® 1 day	Proclear® 1 day
Manufacturer	CooperVision, Inc.	CooperVision, Inc.
Material	omafilcon A	omafilcon A
Replacement schedule	Daily disposable	Daily disposable
Base curve / Diameter, mm	8.7 / 14.2	8.7 / 14.2
Water content	60%	60%
Dk/t (-3.00 D)	28×10^{-9}	28×10^{-9}
Initial power range	−0.75DS to -6.00DS (0.25 steps)	−0.75DS to -6.00DS (0.25 steps)

Children attended a screening visit when informed consent/assent was obtained prior to any study data being collected. The major inclusion/exclusion criteria were:

- Age 8–12 years, inclusive;
- Cycloplegic spherical equivalent auto-refraction in each eye of -0.75D to -4.00D, inclusive;
- Neophyte to contact lenses and no previous exposure to any myopia control treatment;
- Good health with no regular ocular medications;
- No systemic medications that may interfere with contact lens wear, pupil size or accommodative/refractive state;
- No history of ocular or systemic disease that could influence refractive development.

Both the child and the parent/s received instruction on proper contact lens wear and care procedures and the child received practical tuition on how to insert and remove the lenses. After successful dispensing, follow-up visits were scheduled at 1 week, 1 month, 6 months and every 6 months thereafter until 6 years. The children were asked to wear the study lenses bilaterally for a minimum of 10 hours/day, 6 days/week and their compliance to the wearing schedule was confirmed at each visit.

To ensure uniformity across all investigators and sites, investigators were trained on the evaluation, diagnosis codes and reporting of potential adverse events as well as on the biomicroscopy grading scales used in the clinical trial. Children and parents were advised on the signs and symptoms that could indicate a possible adverse response and they were encouraged to call the office or a 24-hour number if they had any concerns. Unscheduled visits were arranged as needed. Any medical complications, both ocular and non-ocular, were reported as adverse events. Examples of non-ocular adverse events that occurred during the clinical trial were ankle fracture, broken arm, and appendectomy. These non-ocular adverse events are unrelated to contact lens usage and are not the subject of this paper and thus results are not presented here.

Ocular adverse events were classified into Serious, Significant or Non-significant adverse events based largely upon ISO11980:2012: *Contact Lens and Lens Care Products – Guidance for Clinical Investigations.* Serious Adverse Events included any vision-threatening conditions or any event that could result in permanent impairment of a body function or permanent damage to a body structure. Significant and Non-significant Adverse Events are not considered Serious Adverse Events and they may or may not require therapeutic treatment and/or temporary cessation of contact lens wear. Table 2 shows the classification table of ocular adverse events provided to investigators as a reference for this clinical trial.

The biomicroscopy assessment involved careful examination of the external adnexa and ocular surface. Corneal infiltrates/opacities were detailed in number, size and position. The grading scales for each variable were accompanied by descriptions in order to aid uniformity across investigators and sites.

The eyelids were everted to assess palpebral hyperaemia and roughness. To assess corneal and conjunctival integrity, sodium fluorescein was instilled, and observations were made using blue light and a yellow barrier filter.

The following assessments were graded using a 0–4 scale and reported in integer steps, with the exception of corneal staining type and conjunctival fluorescein staining which employed 0.5 steps:

- Limbal hyperaemia, single overall grade

Table 2
Adverse event categorisation reference table for investigators.

Serious Adverse Events (SAE)
• Presumed Microbial keratitis (MK)/infectious corneal ulcer • Permanent decrease of ≥ 2 lines in Snellen best spectacle corrected visual acuity (BSCVA) • Central or paracentral corneal opacity • Corneal neovascularisation within the central 6 mm (Grade 4) • Uveitis • Endophthalmitis • Hypopyon • Hyphaema • Iritis • Other serious event
Significant Events
• Peripheral non-infectious ulcer/scar •Symptomatic corneal infiltrative events • Superior epithelial arcuate lesions (SEALs) • Any temporary loss of > 2 lines of BSCVA (for > 2 weeks) •Corneal staining ≥ Grade 3 •Corneal neovascularisation ≥ Grade 2 •Any event which necessitates temporary lens discontinuation ≥ 2 weeks •Other significant event
Non-significant Events
•Non-Significant Infiltrative Events (< Grade 2 and non-symptomatic) •Papillary conjunctivitis Grade 2 (only if a change of 2 grades from baseline) •Blepharitis •Meibomianitis •Contact dermatitis •Localised allergic reactions •Conjunctivitis: bacterial, viral, allergic •Any corneal event which necessitates temporary lens discontinuation ≥ 1 day and < 2 weeks •Other non-significant event

- Bulbar hyperaemia, single overall grade
- Palpebral hyperaemia, central zone of upper and lower
- Palpebral roughness, central zone of upper and lower
- Corneal fluorescein staining in each of the five zones; type, extent, depth
- Conjunctival fluorescein staining in each quadrant
- Corneal vascularisation
- Other findings

The grades represented the following severity levels: 0 = none, 1 = trace, 2 = mild, 3 = moderate and 4 = severe. Corneal staining type, area and depth were graded according to the more explicit descriptions based on the Cornea & Contact Lens Research Unit (now Brien Holden Vision Institute) grading scale. [34] While type, extent and depth of staining were all collected, only the grading of corneal staining type is presented here, because this variable directly grades the severity level of the corneal damage with grade 1 (trace) representing minimal superficial staining and grade 4 (severe) including large abrasions, ulceration or epithelial loss. Extent and depth of staining add descriptive details regarding area of the cornea affected and degree of fluorescein penetration.

Patient-years of lens wear was calculated for each individual from the time of dispensing to the time of discontinuation or completion of the 6-year visit. No discounting was performed for temporary discontinuation of lens wear during the trial. The incidence of adverse responses in patient-years was calculated by dividing the total number of events by the number of patient-years of wear. All ocular adverse events for all subjects are included in the analysis. The 95% confidence intervals were calculated using the method given by Wilson. [35]

3. Results

The baseline demographics for the enrolled subjects have been reported previously. [8] The combined demographics for the entire group are summarised in Table 3.

The accountability of all subjects enrolled in the study is shown in Table 4. Of the 144 subjects randomised to MiSight 1 day or Proclear 1 day, 135 were dispensed lenses and 109 completed the first 3-year phase of the trial. One subject was ineligible to continue to the second phase of the study due to a newly added systemic growth hormone medication with unknown effect on axial elongation. Ninety-two (92) subjects completed the full 6-years.

The reasons for discontinuation are shown in Table 5. Only three discontinuations were related to adverse events, one of these being a non-ocular adverse event (diabetes). Of the two discontinuations for ocular adverse events, only one was related to the contact lenses (infiltrative keratitis). The second was due to an episode of uveitis related to herpes zoster.

Nine subjects (6.3%) were never dispensed lenses and a further 5 subjects (3.5%) discontinued before the first month, primarily due to unacceptable lens fit or inability to cope with lens insertion and removal techniques adequately. Over the remainder of the six years, a further 38 subjects discontinued from the study.

The mean weekday wear time for all evaluable subjects increased from 12.8 h per day at 6 months to 13.9 h per day at six years. The mean number of days per week that the children wore lenses was consistent across the six year with a mean wearing days above 6.5 days per week from one month to the six-year visit. The total patient-years of wear observed over six years was 653 subject-years.

3.1. Ocular adverse events

Forty (40) ocular adverse events were reported in 30 subjects over the course of the six years of follow-up. Twelve (12) of the events were binocular and 28 were monocular. Table 6 provides a summary of all ocular adverse events reported over the six-year period. Each count in this table represents a single adverse event episode. Each adverse event episode is listed under either the monocular or the binocular column, according to whether one or both eyes were affected. The final column indicates how many of the presentations were considered by the investigator to be potentially contact lens wear related, based on history and presentation. The majority (93%) of the events were considered as Non-significant Adverse Events. Only one ocular Serious Adverse Event was reported, a uveitis associated with herpes zoster which occurred in Year 5. This subject had experienced two previous events, superficial punctate staining (Year 4) and blurry vision (Year 5). All three events were in the subject's right eye only. Two other events were considered as Significant Adverse Events. Both were new peripheral corneal scars noted at a follow-up visit. One of the subjects (Year 4) recalled some irritation two months prior to the scheduled visit at which the scar was noted. The second subject (Year 6) was asymptomatic at a scheduled visit but the investigator noted a small embedded foreign body and a new peripheral scar. There were 4 reports of minor infiltrative events with no associated symptoms and all were noted at scheduled visits.

Across the six years, there were two occasions of a subject being discontinued by the investigator due to an ocular adverse event. One was the case of uveitis which was considered not to be contact lens

Table 3
Demographic data at baseline, n = 144.

Age	10.1 ± 1.4 years (range 8–12)
Sex	69F:75M
Ethnicity	East Asian: 34 West Asian: 12 Caucasian: 79 Other: 6 Mixed: 13
Cycloplegic spherical equivalent auto-refraction	−2.11D ± 0.79 (range -0.77 to -4.00)

Table 4
Subject accountability across six years.

	Completed Visit	Discontinued
Enrollment	144	0
Dispensed contact lenses	135	9
Completed first month	130	5
Completed year 1	122	8
Completed year 2	117	5
Completed year 3	109	8
Completed year 4	100	9
Completed year 5	98	2
Completed year 6	92	6

Table 5
Discontinuations across the 6 years, total n = 52.

Reason	# of Subjects	Time of Occurrence	Count	Lens- related?
Adverse event – Ocular	2	Year 3 (infiltrative keratitis)	1	Y
		Year 5 (uveitis)	1	N
Adverse event - Non-ocular	1	Year 3 (diabetes)	1	N
Unacceptable Lens Fit	7	First month	6	Y
		Year 4	1	Y
Lens handling	6	First month	5	Y
		Year 1	1	Y
Dissatisfaction with comfort	5	First month	1	Y
		Year 1	1	Y
		Year 2	1	Y
		Year 3	1	Y
		Year 4	1	Y
Dissatisfaction with vision or uncorrected astigmatism	7	Year 2	1	Y
		Year 4	3	Y
		Year 6	3	Y
Not happy with lens wear or prefers spectacle	5	Year 1	1	Y
		Year 3	1	Y
		Year 4	2	Y
		Year 6	1	Y
Protocol prohibited medication	3	First month	1	N
		Year 2	1	N
		Year 4	1	N
Motivation/ Inconvenience	7	Year 1	4	N
		Year 2	2	N
		Year 3	1	N
Relocated	5	Year 3	2	N
		Year 4	1	N
		Year 6	2	N
Lost-to-Follow-Up	4	First month	1	Unknown
		Year 1	1	Unknown
		Year 3	1	Unknown
		Year 5	1	Unknown
TOTAL	52			

related, and the other was a subject who experienced a second occurrence of asymptomatic infiltrative keratitis which was considered possibly contact lens related.

Approximately one-third (13/40) of these ocular adverse events were reported in the first year of wear, with 6/13 of these reported in the first month. This may be partially due to minor occurrences during adaptation to lens wear but is also likely an effect of the increased frequency of scheduled visits at study start-up. Over the course of the six years, 40% of the adverse events were minor complications noted at scheduled visits; examples of such minor events were tarsal hyperemia, irritation from a lens trapped under the upper lid, and a single asymptomatic infiltrate associated with viral cold. Investigators reported that 45% of the ocular event episodes were not lens-related. All of the ocular adverse events are shown in Table 6, including those that were minor complications and those not considered to be contact lens related.

Table 6
Study ocular adverse event summary.

	Monocular (each count – 1 eye)	Binocular (each count – 2 eyes)	# of all events considered as potentially CL related
Serious Events (n = 1)			
• Uveitis (associated with herpes zoster)	1	0	0
Significant Events (n = 2)			
• New peripheral scar	2	0	2
Non-Significant Events (n = 37)			
• Non-Significant Infiltrative Events (<Grade 2 and non-symptomatic)	4	0	3
• Papillary conjunctivitis Grade ≥2 (only if a change of 2 grades from baseline)	1	1	1
• Blepharitis	0	1	0
• Meibomianitis	1	1	0
• Localised allergic reactions	0	1	1
• Conjunctivitis: bacterial, viral, allergic	1	1	0
• Any corneal event which necessitates temporary lens discontinuation >1 day and <2 weeks *Foreign body; superficial punctate keratitis; mild pannus; corneal staining*	5	1	5
• Other Non-significant event *Eye irritation; lens removal difficulty; mild dryness; tarsal hyperaemia; subconjunctival haemorrhage, small epithelial opacity; episcleritis; asthenopia; burning/stinging; foreign body; asymptomatic red eye; blurry vision*	12	7	10

Fig. 1 shows the number of subjects enrolled at each age and the age at which all ocular adverse events were noted. The mean age at adverse event presentation was 12.6 ± 2.0 years of age. No ocular adverse events were observed in children under 10 years of age.

There were no contact lens related corneal infections reported. Four contact lens related corneal infiltrative events were reported in three subjects over 6 years. Based on 653 subject-years of observation, this represents a crude incidence rate for corneal infiltrative events of 0.61% or 6.1 per 1000 wearing years (95% CI: 0.24%–1.57%).

3.2. Ocular health: biomicroscopy findings

Table 7 summarises the biomicroscopy evaluations from all visits, scheduled and unscheduled, across the entire six years. The majority of evaluations (99% of total findings) were Grade 0–1. The highest

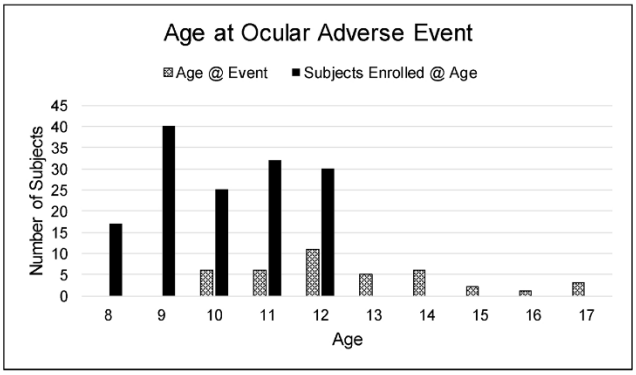


Fig. 1. Age at ocular adverse event presentation (n − 40), age of enrolment in study (n − 144).

frequency of findings greater than zero were for tarsal hyperaemia, tarsal roughness, and bulbar hyperaemia. There were only five incidents of a biomicroscopy finding grade higher than 2 (mild) across all the scheduled study visits; one limbal hyperemia, two bulbar hyperemia, one tarsal hyperemia, and one tarsal roughness.

A comparison of the reported findings at the Baseline Visit, prior to any contact lens wear, and at the Final Visit (6-year visit or exit visit for discontinued subjects) shows that there was no change in ocular physiology signs over the contact lens wearing period.

4. Discussion

This clinical trial was designed to assess the efficacy of MiSight 1 day for controlling myopia progression and to assess the safety of soft contact lens wear in a young neophyte cohort, fitted at age 8–12 and followed through early adolescence. The lenses in this trial were worn on a daily disposable modality, which has long been the recommended modality in children because it avoids compliance concerns related to cleaning, storage and replacement, [36] and is considered to be associated with fewer adverse events in a young population [22,23,26,29].

This study is unique in that it is a long-term prospective clinical trial allowing multi-year assessment of the safety of this daily disposable soft lens in this young population. This six-year clinical trial represents the equivalent of 653 lens-wearing years. In order to advise parents and children considering soft lenses as a myopia control strategy, eyecare practitioners should understand how children respond in their early years of contact lens wear. Clinical trials provide a more detailed and extensive assessment of safety than retrospective chart reviews and routine clinical practice, largely due to the increased frequency of study visits and the more detailed documentation requirements.

Contact lens wear safety can be further assessed by reviewing discontinuations, together with the reasons behind them. Ninety-two subjects completed the full six years, representing 68% of the subjects that were originally found eligible to participate, with only one discontinuation due to a lens-related adverse event. Overall, this would be considered a high retention rate for such a long clinical trial with a strict visit schedule and it compares favourably with two recent trials involving children wearing daily disposable contact lenses for myopia control; in the first year of a 2 year trial of a novel myopia control daily disposable lens, Cheng et al. [33] reported 21 (17%) children discontinued and Ruiz-Pomeda et al. [28] reported high retention across a two year trial of the MiSight 1 day lens, with only five of the 44 children discontinuing (11%). A recent publication, by Walline et al. [37], on monthly replacement lenses worn for myopia control, reported a very high 98% retention at the end of the three year trial.

In this study, more subjects discontinued during the first month (14 children; 9.7%) than during any of the subsequent single year periods. Most of these early discontinuations were due to inadequate lens fit or an inability to handle the lenses. These reasons have previously been reported to be among the most common reasons for early contact lens drop-out among the general population. [38] The rest of the discontinuations were a mix of lens-related reasons, like lens discomfort or preferring the appearance of spectacles, and other reasons, like relocation, starting a prohibited medication or inability to maintain the study schedule.

Just over half of the ocular adverse events were considered to be contact lens related (22/40, Table 6). Practitioners are well equipped to deal with ocular adverse events such as 'dryness' and 'lens stinging on insertion'. However, events of corneal infection or inflammation pose greater concerns. There were no cases of microbial keratitis in the study.

The discontinuation rate of the younger population in this study compares favorably with studies of neophyte adults fitted into daily disposable lens wear. In a recent study in which the neophytes adults were fit with a silicone hydrogel daily disposable, there were premature discontinuations in 39.5% (15/38) of the lens wearing population within the one-year study duration. [39] Of these 40% (6/15) discontinued at or before the one-month visit. Another study, that looked at neophyte adult wearers over one year, this time with daily disposable hydrogel lens wear. [40] observed discontinuations in 33% (46/139), with 10% (14/139) occurring in the first month.

In this study there were no cases of microbial keratitis, and the rate of corneal infiltrative events was 0.61% (95% CI: 0.24%–1.57%). Comparing adverse event reporting across studies can be challenging due to varying study designs, protocol definitions and methods of reporting. This particular protocol required all negative experiences to be captured as adverse events and it is quite possible that some of the events reported in this trial, such as 'mild dryness', 'lens caught under lid' and 'lens stinging on insertion', would not be reported as adverse events in all trials. Similarly, comparing adverse events in clinical trials to those reported in retrospective chart review or survey studies can be problematic because the latter capture only those adverse events that prompted a visit to the clinic.

Chalmers et al. [22] used a registry/survey methodology to determine ocular adverse event rates in 1171 predominantly adult daily disposable lens wearers over one year. Specifically, they investigated incidences of lens related 'red or painful eye' events that prompted an office visit and reported an annualised rate of 1.6% (95% CI: 0.8–3.2, based on 498 lens wear years) for silicone hydrogel lenses and 0.6% (95% CI: 0.2–1.9, based on 471 lens wear years) for hydrogel lenses. They also reported rates for infiltrative events of 0.4% in silicone

Table 7
Summary of biomicroscopy findings across all study visits over six years. Comparison of baseline visit to final visit (n – 288 eyes) (0 – none; 1–trace; 2–mild; 3=moderate; 4=severe).

Variable	Grade	Findings across all Visits		Findings at all Baseline Visits		Findings at all Final Visits	
		Count of eyes	**% of total**	**Count of eyes**	**% of total**	**Count of eyes**	**% of total**
Limbal hyperaemia	**0**	2460	76	199	69	212	74
	1	754	23	89	31	58	20
	2	7	0.2	0	0	0	0
	3	1	0.03	0	0	0	0
	4	0	0	0	0	0	0
						18 missing[#]	6
Bulbar hyperaemia	**0**	2071	64	144	50	179	62
	1	1121	35	142	49	89	31
	2	28	1	2	1	2	0
	3	2	0.1	0	0	0	0
	4	0	0	0	0	0	0
						18 missing[#]	6
Tarsal hyperaemia	**0**	1878	57	156	54	167	58
	1	1320	40	106	37	114	40
	2	82	3	26	9	4	1
	3	1	0.03	0	0	0	0
	4	0	0	0	0	0	0
						3 missing[#]	1
Tarsal roughness	**0**	1895	58	140	49	174	60
	1	1329	41	134	47	108	38
	2	56	2	14	5	3	1
	3	1	0.03	0	0	0	0
	4	0	0	0	0	0	0
						3 missing[#]	1
Corneal staining type[*]	**0**	2437	74	234	81	233	81
	0.5	605	18	38	13	45	16
	1	221	7	14	5	6	2
	1.5	9	0.3	1	0.3	1	0
	2	13	0.4	1	0.3	1	0
	all >2	0	0	0	0	0	0
						2 missing[#]	1
Conjunctival staining[*]	**0**	2431	74	237	82	233	81
	0.5	642	20	40	14	43	15
	1	182	6	9	3	9	3
	1.5	28	1	2	1	1	0
	2	2	0.1	0	0	0	0
	all >2	0	0	0	0	0	0
						2 missing[#]	1
Corneal vascularisation	**0**	3200	98	288	100	272	94
	1	81	3	0	0	13	5
	2	0	0	0	0	0	0
	all >2	0	0	0	0	0	0
						3 missing[#]	1
Other findings	**0**	3250	99	284	99	284	99
	1	27	1	2	0.7	0	0
	2	3	0.1	2	0.7	0	0
	all >2	0	0	0	0	0	0
						4 missing[#]	1

[*] The highest staining grade of all the regions, per subject, is reported.
[#] Data was missing from data collection documents.

hydrogels and 0% in hydrogels. In contrast to the current study, these subjects were only followed for one year, and the adverse events captured were only those that prompted an office visit, not discovered at scheduled study visits that naturally increase the discovery of asymptomatic events.

The Contact Lens Assessment in Youth (CLAY) [25] study retrospectively reviewed charts from 3549 patients for the presence of infiltrative events. There were 260 subjects in the 8–12-year-old cohort, similar to our enrolled cohort. The rate of significant infiltrative events was 0.97% (95% CI: 0.03%–2.35%) in this population. However, in the 13–17-year olds, closer to the age of our cohort at the end of six years the reported rate was 3.35%. This rose even higher in the 18–25-year-old group. Our study would suggest a similar rate (0.61%) of infiltrative events to the younger cohort in the CLAY study, with the obvious considerations that the children in our study were closely supervised and only prescribed in a daily disposable modality.

A more recent publication [30] combined retrospective chart review data (sample of 782 charts) with clinical trial data for a total of 963

children aged 8–17 years who had worn various soft lenses for an average of 2.8 years; a total of 2713 lens wearing years. The authors reported an annual incidence rate of 0.66% for all inflammatory adverse events (which included infiltrative keratitis, contact lens associate peripheral ulcer and contact lens related acute red eye) which is very similar to the 0.61% rate for infiltrative events reported in this study.

Other multi-year clinical trials involving children have reported a range of results for adverse events. In trials involving daily disposable soft lenses, Cheng et al. [33] and Ruiz-Pomeda et al. [28] each reported just two subjects with non-serious, non-device related ocular adverse events, in approximately 100 and 80 lens wearing years, respectively. Walline et al. [32] reported five ocular, lens related adverse events across their three year trial, equivalent to approximately 600 daily disposable lens wear years. In a more recent trial, Walline et al. [37] followed almost 300 children wearing two different monthly replacement soft lenses for three years and the results indicated a device related, moderate severity, ocular adverse event rate of approximately 4 per 100 lens-wearing years and an infiltrative event rate of approximately 2.0%. Sankaridurg et al. [27] fitted 240 children with monthly replacement silicone hydrogel lenses in a daily wear modality for two years and reported a rate of 14.2 ocular, device related adverse events per 100 lens-wearing years. They also reported 25 corneal infiltrative events, which approximates to a rate of over 6 per 100 lens-wearing years. These last two studies reported higher rates than was found in this trial, but it has been reported previously that re-useable contact lenses are associated with a higher rate of adverse events than the daily disposable modality. [22,23,26,29,31] The results of this trial are a valuable addition to this literature to provide more understanding of the response of children to daily disposable lens wear.

The ocular physiological response of this child/adolescent population was assessed using detailed biomicroscopy assessments at all study visits. The majority of the biomicroscopy assessments were grade zero. Considering assessments at all visits across the entire period, including unscheduled visits associated with adverse events, there were only five biomicroscopy findings greater than grade 2 (mild). Given the full-time wear schedule of hydrogel daily disposable lenses, any hypoxic changes were of interest. Corneal neovascularisation and limbal hyperaemia are recognised as indicators of corneal hypoxia [41] and throughout the entire study period, just 2% of all these assessments were greater than grade 0. There were sporadic reports of grade 1 neovascularisation (trace congestion and dilation of limbal vessels / single vessels extension <1.0 mm) and less than 1% of the reports of limbal hyperaemia were greater than grade 1, with only a single incidence of grade 3 reported. There was no change noted between baseline and final visit in any corneal sign. These results show there was no clinical evidence of hypoxic or physiological changes with this population wearing the omafilcon A hydrogel daily disposable lenses. This supports other literature that have reported no clinically relevant hypoxic changes with a healthy population wearing hydrogel lenses in a daily wear, daily disposable modality. [42–44] Hypoxic changes were not expected because the oxygen transmission through these thin lenses of low/mid myopic powers meets the requirements for daily wear in an adult population, and it is reassuring to see this confirmed within this paediatric population.

It was of interest to note the relatively high baseline visit incidence of grade 1 bulbar hyperaemia, tarsal hyperaemia and tarsal roughness, compared to other biomicroscopy variables. It may be intuitive to expect children in this age group to present with more 'quiet' eyes. While it was encouraging to see these incidences reduce over the study period, this finding serves as a reminder to practitioners that lid eversion should be a routine part of the paediatric assessment.

Overall, the children in this clinical trial were successful contact lens wearers. They achieved relatively long wearing hours, exhibited low grades of and clinically insignificant biomicroscopy findings and there were no lens-related serious adverse events. The reasons for lens wearing success are often multifactorial, with lens fit, lens material/surface and subject habits all contributing. A good lens fit was an important criterion for continuing in this study and therefore a poor fit resulted in the subject being discontinued from the study. This approach of not accepting a sub-optimal lens fit is encouraged in clinical practice to avoid mechanical, lens related adverse responses. The surface of the lens is also an important factor in the physiological response. The omafilcon A material with MiSight 1 day and Proclear 1 day has been shown to have good resistance to lipid and protein deposition and it also demonstrates low dehydration properties. [45,46]

It could be argued that there are aspects about clinical trials that lead to higher retention and success than the clinical practice setting. The regular visit schedule in a clinical trial allows frequent training of both the chid and the parent on good contact lens habits, and it has been suggested that retraining will improve outcomes. [29] Compliance with lens replacement is also likely to be improved when the products are provided at no charge, as they were in this trial. Compliance with the lens replacement schedule has been shown to be a risk factor for lens related complications, as has overnight wear. [17,18,21,25] Children receive additional protection from parents, who will generally be vigilant to ensure overnight wear and napping do not occur, thereby helping to reduce adverse events and improve success rates. Walline et al. [2] has reported that there is no difference in adverse events in the ten year period post lens fitting, between children who were fit younger than thirteen, compared to those fit as a teenager. Indeed there have been several reports that suggest the under thirteen age group may be less at risk for contact lens related complications. [6,25] All of these points are reassuring as we are faced with treating the ever-younger, fast progressing myope.

The safety and ocular health results of this study can be considered relevant to future cohorts of children fit with hydrogel, daily disposable contact lenses for myopia control, because the lenses were worn full-time, just as they will be worn for any future myopia control contact lens design. There was a high retention rate in this age group across the six years.

5. Conclusions

The omafilcon A daily disposable contact lenses were well accepted in full-time wear and performed well in this 8–12-year-old neophyte cohort across six years. There were no contact lens related serious adverse events. Discontinuations and biomicroscopy data were comparable with other daily disposable clinical trials in a similarly aged population. These results suggest that children as young as eight years of age can successfully wear daily disposable, hydrogel contact lenses for multiple consecutive years, making these lenses a viable and safe method for delivering optical management of myopia progression control.

6. Statements of significance

A report of ocular health data and safety profile from a longitudinal clinical trial involving a neophyte paediatric population wearing daily disposable hydrogel soft contact lenses over a six-year period.

Funding

This manuscript and the clinical trial reported herein were supported by research funds from CooperVision, Inc.

Acknowledgements

The clinical trial reported in this manuscript was sponsored by CooperVision, Inc. The authors would like to acknowledge the members of the 'MiSight® 1-day Clinical Study Group':

Visioncare Research Limited, Farnham, Surrey, United Kingdom: Graeme Young (Medical Monitor), Chris Hunt (Statistician), Ruth Craven (Clinical Research Manager), Susanna Jones (Project Manager),

Michael Spyridon, Tom Boyes, Sarah McCready & Kristine Roslin (Clinical Research Associates), Shaun Peters (Clinical Research Coordinator), Tricia Riley, Emma Lyle, Glenis Rogers & Janet Faulks (Data Entry).

University of Minho, CEOR Lab: José Manuel González-Méijome (Principal Investigator), Sofia Cláudia Peixoto-de-Matos, Ana Maria Fernandes de Pinho Dias, Helena Isabel Ferreira-Neves, Daniela Patricia Lopes-Ferreira & Ana Amorim-de-Sousa (Co- Investigators).

Aston University Ophthalmic Research Group: Nicola Logan (Principal Investigator), Susie Jones, Fi Cruickshank & Manbir Nagra (Co-Investigators).

National University Health System, Ophthalmology Department, Singapore: Seang Mei Saw (Chief Investigator), Cheryl Ngo (Principal Investigator 2014-current, Co-Investigator 2012-2014), Inez By Wong (Principal Investigator, 2012-2014), Ivy Law (Administrative Manager), Ray Manotosh, Michelle Lim & Amanda Lim (Co-Investigators), Anny Leow (Coordinator).

University of Waterloo School of Optometry, Waterloo, Canada: Lyndon Jones (Principal Investigator), Debbie Jones, Jill Woods, Lindsay Paquette, Mike Yang & Karen Walsh (Co- Investigators), Jane Johnson, Marina Simpson, Leona Voss, Debbie Murray & Amanda McIntosh (Assistants).

References

[1] Morgan PB, Woods CA, Tranoudis IG, Efron N, Jones L. International contact lens prescribing in 2019. Contact Lens Spectrum. 2020;(35):26–32.
[2] Walline JJ, Lorenz KO, Nichols JJ. Long-term contact lens wear of children and teens. Eye Contact Lens 2013;39:283–9.
[3] Bullimore MA. Myopia control: the time is now. Ophthalmic Physiol Opt 2014;34:263–6.
[4] Paquette L, Jones DA, Sears M, Nandakumar K, Woods CA. Contact lens fitting and training in a child and youth population. Cont Lens Anterior Eye 2015;38:419–23.
[5] Walline JJ. Myopia control: a review. Eye Contact Lens 2016;42:3–8.
[6] Bullimore MA. The safety of Soft contact lenses in children. Optom Vis Sci 2017;94:638–46.
[7] Sankaridurg P. Contact lenses to slow progression of myopia. Clin Exp Optom 2017;100:432–7.
[8] Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young G. A 3-year randomized clinical trial of MiSight lenses for myopia control. Optom Vis Sci 2019;96:556–67.
[9] Sankaridurg P, Bakaraju RC, Naduvilath T, Chen X, Weng R, Tilia D, et al. Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. Ophthalmic Physiol Opt 2019;39:294–307.
[10] Wolffsohn JS, Calossi A, Cho P, Gifford K, Jones L, Jones D, et al. Global trends in myopia management attitudes and strategies in clinical practice - 2019 Update. Cont Lens Anterior Eye 2020;(43):9–17.
[11] Walline JJ, Jones LA, Rah MJ, Manny RE, Berntsen DA, Chitkara M, et al. Contact Lenses in Pediatrics (CLIP) Study: chair time and ocular health. Optom Vis Sci 2007;84:896–902.
[12] Sindt CW, Riley CM. Practitioner attitudes on children and contact lenses. Optometry 2011;82:44–5.
[13] Efron N, Morgan PB, Woods CA, Santodomingo-Rubido J, Nichols JJ. International Contact Lens prescribing Survey C. International survey of contact lens fitting for myopia control in children. Cont Lens Anterior Eye 2020;43:4–8.
[14] Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 2016;123:1036–42.
[15] Dumbleton K. Noninflammatory silicone hydrogel contact lens complications. Eye Contact Lens 2003;29. S186-9; discussion S90-1, S92-4.
[16] Stapleton F, Stretton S, Papas E, Skotnitsky C, Sweeney DF. Silicone hydrogel contact lenses and the ocular surface. Ocul Surf 2006;4:24–43.
[17] Stapleton F, Keay L, Jalbert I, Cole N. The epidemiology of contact lens related infiltrates. Optom Vis Sci 2007;84:257–72.
[18] Szczotka-Flynn L, Diaz M. Risk of corneal inflammatory events with silicone hydrogel and low dk hydrogel extended contact lens wear: a meta-analysis. Optom Vis Sci 2007;84:247–56.
[19] Dart JK, Radford CF, Minassian D, Verma S, Stapleton F. Risk factors for microbial keratitis with contemporary contact lenses: a case-control study. Ophthalmology 2008;115:1647–54. 54 e1-3.
[20] Keay L, Edwards K, Stapleton F. Signs, symptoms, and comorbidities in contact lens-related microbial keratitis. Optom Vis Sci 2009;86:803–9.
[21] Stapleton F, Edwards K, Keay L, Naduvilath T, Dart JK, Brian G, et al. Risk factors for moderate and severe microbial keratitis in daily wear contact lens users. Ophthalmology 2012;119:1516–21.
[22] Chalmers RL, Hickson-Curran SB, Keay L, Gleason WJ, Albright R. Rates of adverse events with hydrogel and silicone hydrogel daily disposable lenses in a large postmarket surveillance registry: the TEMPO Registry. Invest Ophthalmol Vis Sci 2015;56:654–63.
[23] Lim CH, Carnt NA, Farook M, Lam J, Tan DT, Mehta JS, et al. Risk factors for contact lens-related microbial keratitis in Singapore. Eye (Lond). 2016;30:447–55.
[24] Li L, Moody K, Tan DT, Yew KC, Ming PY, Long QB. Contact lenses in pediatrics study in Singapore. Eye Contact Lens 2009;35:188–95.
[25] Chalmers RL, Wagner H, Mitchell GL, Lam DY, Kinoshita BT, Jansen ME, et al. Age and other risk factors for corneal infiltrative and inflammatory events in young soft contact lens wearers from the Contact Lens Assessment in Youth (CLAY) study. Invest Ophthalmol Vis Sci 2011;52:6690–6.
[26] Wagner H, Chalmers RL, Mitchell GL, Jansen ME, Kinoshita BT, Lam DY, et al. Risk factors for interruption to soft contact lens wear in children and young adults. Optom Vis Sci 2011;88:973–80.
[27] Sankaridurg P, Chen X, Naduvilath T, Lazon de la Jara P, Lin Z, Li L, et al. Adverse events during 2 years of daily wear of silicone hydrogels in children. Optom Vis Sci 2013;90:961–9.
[28] Ruiz-Pomeda A, Perez-Sanchez B, Prieto-Garrido FL, Gutierrez-Ortega R, Villa-Collar C. MiSight assessment study Spain: adverse events, tear film osmolarity, and discontinuations. Eye Contact Lens 2018;44(Suppl 2). S180-S6.
[29] Sorbara L, Zimmerman AB, Mitchell GL, Richdale K, Lam DY, Kinoshita BT, et al. Multicenter testing of a risk assessment survey for Soft contact Lens wearers with adverse events: a contact Lens assessment in youth study. Eye Contact Lens 2018;44:21–8.
[30] Chalmers RLMJ, Chamberlain P, Keay L. Retrospective cohort study of safety of pediatric soft contact lens wear: the ReCSS study. Invest Ophthalmol Vis Sci 2020;61:5215.
[31] Chalmers RL, Keay L, McNally J, Kern J. Multicenter case-control study of the role of lens materials and care products on the development of corneal infiltrates. Optom Vis Sci 2012;89:316–25.
[32] Walline JJ, Jones LA, Sinnott L, Manny RE, Gaume A, Rah MJ, et al. A randomized trial of the effect of soft contact lenses on myopia progression in children. Invest Ophthalmol Vis Sci 2008;49:4702–6.
[33] Cheng X, Xu J, Chehab K, Exford J, Brennan N. Soft contact lenses with positive spherical aberration for myopia control. Optom Vis Sci 2016;93:353–66.
[34] Terry RL, Schnider CM, Holden BA, Cornish R, Grant T, Sweeney D, et al. CCLRU standards for success of daily and extended wear contact lenses. Optom Vis Sci 1993;70:234–43.
[35] Wilson EB. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc 1927;22:209–12.
[36] Walline JJ, Long S, Zadnik K. Daily disposable contact lens wear in myopic children. Optom Vis Sci 2004;81:255–9.
[37] Walline JJ, Walker MK, Mutti DO, Jones-Jordan LA, Sinnott LT, Giannoni AG, et al. Effect of high add power, medium add power, or single-vision contact lenses on myopia progression in children: the BLINK randomized clinical trial. JAMA 2020;324(6):571–80.
[38] Sulley A, Young G, Hunt C. Factors in the success of new contact lens wearers. Cont Lens Anterior Eye 2017;40:15–24.
[39] Morgan PB, Chamberlain P, Moody K, Maldonado-Codina C. Ocular physiology and comfort in neophyte subjects fitted with daily disposable silicone hydrogel contact lenses. Contact Lens Anterior Eye 2013:36.
[40] Sankaridurg PR, Sweeney DF, Holden BA, Naduvilath T, Velala I, Gora R, et al. Comparison of adverse events with daily disposable hydrogels and spectacle wear: results from a 12-month prospective clinical trial. Ophthalmology 2003;110:2327–34.
[41] Sweeney DF. Have silicone hydrogel lenses eliminated hypoxia? Eye Contact Lens 2013;39:53–60.
[42] Moezzi AM, Varikooty J, Schulze M, Ngo W, Lorenz KO, Boree D, et al. Corneal swelling with cosmetic etafilcon a lenses versus No Lens Wear. Optom Vis Sci 2016;93:619–28.
[43] Moezzi AM, Varikooty J, Luensmann D, Schulze MM, Ng A, Karkkainen T, et al. The short-term physiological impact of switching reusable silicone hydrogel wearers into a hydrogel daily disposable multifocal. Clin Ophthalmol 2019;13:1193–202.
[44] Diec J, Tilia D, Thomas V. Comparison of silicone hydrogel and hydrogel daily disposable contact lenses. Eye Contact Lens 2018;44(Suppl 1). S167-S72.
[45] Young G, Bowers R, Hall B, Port M. Clinical comparison of Omafilcon A with four control materials. CLAO J 1997;23:249–58.
[46] Lemp MA, Caffery B, Lebow K, Lembach R, Park J, Foulks G, et al. Omafilcon A (Proclear) soft contact lenses in a dry eye population. CLAO J 1999;25:40–7.

5.3. Publication: Adverse event rates in the retrospective cohort study of safety of paediatric soft contact lens wear: the ReCSS study

OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS

Ophthalmic and Physiological Optics ISSN 0275-5408

Adverse event rates in the retrospective cohort study of safety of paediatric soft contact lens wear: the ReCSS study

Robin L Chalmers[1], John J McNally[2], Paul Chamberlain[2] and Lisa Keay[3,4]

[1]Clinical Trial Consultant, Atlanta, USA, [2]CooperVision, Inc., Pleasanton, USA, [3]School of Optometry and Vision Science, UNSW Sydney, Sydney, NSW, Australia, and [4]The George Institute for Global Health, UNSW Sydney, Sydney, NSW, Australia

Citation information: Chalmers RL, McNally JJ, Chamberlain P, & Keay L. Adverse event rates in the retrospective cohort study of safety of paediatric soft contact lens wear: the ReCSS study. *Ophthalmic Physiol Opt*. 2021; 41: 84–92. https://doi.org/10.1111/opo.12753

Keywords: myopia control contact lenses, paediatric, adverse events, epidemiology

Correspondence: Robin L Chalmers
E-mail address: Chalmers2097@gmail.com

Received: 29 July 2020; In Revised form: 10 September 2020; Accepted: 30 September 2020; Published online: 11 November 2020

Abstract

Purpose: To ascertain the safety of soft contact lens (SCL) wear in children through a retrospective chart review including real-world clinical practice settings.

Methods: The study reviewed clinical charts from 963 children: 782 patients in 7 US eye care clinics and 181 subjects from 2 international randomised clinical trials (RCTs). Subjects were first fitted while 8–12 years old with various SCL designs, prescriptions and replacement schedules, and observed through to age 16. Clinical records from visits with potential adverse events (AEs) were electronically scanned and reviewed to consensus by an Adjudication Panel.

Results: The study encompassed 2713 years-of-wear and 4611 contact lens visits. The cohort was 46% male, 60% were first fitted with daily disposable SCLs, the average age at first fitting was 10.5 years old, with a mean of 2.8 ± 1.5 years-of-wear of follow-up observed. There were 122 potential ocular AEs observed from 118/963 (12.2%) subjects; the annualised rate of non-infectious inflammatory AEs was 0.66%/year (95% CI 0.39–1.05) and 0.48%/year (0.25–0.82) for contact lens papillary conjunctivitis. After adjudication, two presumed or probable microbial keratitis (MK) cases were identified, a rate of 7.4/10 000 years-of-wear (95% CI 1.8–29.6). Both were in teenage boys and one resulted in a small scar without loss of visual acuity.

Conclusion: This study estimated the MK rate and the rate of other inflammatory AEs in a cohort of SCL wearers from 8 through to 16 years of age. Both rates are comparable to established rates among adults wearing SCLs.

Introduction

The efficacy of myopia control soft contact lenses to slow the progression of myopia has been demonstrated in a number of clinical trials to date.[1–6] In 2019, the US Food & Drug Administration (FDA) approved the first soft contact lens (MiSight® 1 Day) indicated to slow the progression of myopia in children who, at the initiation of treatment, are 8–12 years of age.[7] These developments will increase the use of myopia control soft contact lenses around the world. Clinical prescribing of soft contact lenses as a myopia control strategy will continue to increase overall soft contact lens (SCL) use in children, starting at 8–12 years of age as they experience the onset of myopia.[8,9] Despite well-established information on the safety of SCLs in adults, the rate of serious adverse events (AEs) with SCL use in this younger age group has not been widely studied, since there was no specific indication for their use in the paediatric population before the introduction of myopia control soft contact lenses.

Microbial keratitis (MK) related to SCL wear is the most serious AE experienced by SCL wearers, and in some instances may be sight-threatening.[10] Fortunately, the condition is rare, but it must be differentiated from other non-infectious corneal inflammatory events (CIEs), as MK and CIEs may require different pharmaceutical management

and clinical care until the events are resolved.[11] The relative safety of SCL wear across ages 8 33 years was the focus of a large retrospective chart review conducted in 2009 by the Contact Lens Assessment in Youth (CLAY) Study Team.[12] [14] That investigation over-sampled for young patients aged 8 12 years old, and found that although the types of SCL-related complications in the 8- to 12-year olds was similar to that of older SCL wearers, the overall AE and CIE rates were lowest in this age group, and was less than one third of the rate for 15- to 25-year-olds[13–14] This relatively low rate of complications in young SCL wearers echoed findings from an earlier study of SCL wear between 2005 and 2008, where SCL wearers from 8–12 years old again showed a much lower rate of eye care visits related to complications from SCL wear compared to older wearers.[15] Those studies were designed to estimate the rate of corneal infiltrative events (CIEs) and were not of sufficient size to determine the rate of rarer, sight-threatening microbial keratitis (MK) in the 8- to 12-year age group. The CLAY study included 243 children who were fitted between 8–12 years old, and the study of private practices had fewer than 30 wearers who were fitted at that age.[13,15]

The purpose of this study was to ascertain the safety of SCL wear in children through a retrospective chart review that included real-world clinical practice settings and data from randomised, controlled clinical trials.

Methods

The current study was a retrospective cohort chart review that included wearers of all types of SCLs who were fitted while they were aged 8–12 years (inclusive). It was specifically designed to be of sufficient size to estimate the rate of MK in wearers initially fitted at that age, and to characterise the AEs experienced by children and young adolescent SCL wearers. The retrospective cohort chart review utilises many of the approaches outlined by the US Food and Drug Administration's 2017 Guidance – Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices.[16] Clinical charts from young SCL wearers in seven geographically-diverse US eye care clinics, and case report forms from two randomised clinical trials (RCTs) of MiSight® 1 Day SCLs (CooperVision, www.coopervision.co.uk)[4,5] conducted in Canada, Portugal, Singapore, Spain and the United Kingdom, were retrospectively reviewed to document the safety of SCL wear in children.

Eligible data were included from children aged 8–16 who were originally fitted with SCLs while they were 8–12 years old (inclusive). For each visit documented in the clinical charts and in the case report forms, the wearer's age, visit date, chief complaint, evidence of continued SCL use, visual acuity with SCLs and results of biomicroscopy were recorded. The details of which SCLs they were wearing (refractive power, brand and replacement schedule) were only captured at the first visit. The study was expressly designed to study safety with SCL wear. No attempt to measure the progression of refractive error was made, knowing that it could not be measured precisely through a chart review.

Community sites were invited to participate in a chart review study of paediatric SCL wearers. To minimise any bias in chart selection, the sites were not informed that the primary focus was a review of adverse events. To ensure an adequate sample of children in the appropriate age group and to minimise missing data through treatment outside of the practice, sites were required to be practising primary eye care, be licenced to treat complications associated with SCL wear and to have a sufficient SCL patient population who were fitted while 8 12 years old. Adequate record keeping was mandatory and the Principal Site Investigators were trained in protecting the privacy of human research participants. Sites were chosen to include various practice settings, locations, sizes and geography. *Table* S1 lists the sites and investigators in the community clinics.

For the review of patient charts in community eye care clinics, an Institutional Review Board (IRB) Waiver of Informed Consent was obtained from Sterling IRB (SIRB#6156). Subjects were identified onsite by the research team using site-specific search methods since each office's search capabilities differed depending on their electronic medical record systems. In general, lists of patients who were in the age category were reviewed to find those who were fitted with SCLs before they turned 13 years old by searching backward in their medical records. All visits until they reached their 17th birthday were documented. If a child had not attended a visit in the previous nine months, the family was contacted via e-mail or post in order to determine whether the child was still wearing SCLs. They were also asked whether they had "experienced any red or painful eye that required a visit to an eye doctor or emergency room since their last visit" to the prescribing practice. If so, records would be obtained from that treating office. Two sites did not agree to this active follow-up of their patients.

The RCT audit included two investigations; the longitudinal study of MiSight® 1 Day SCLs[4] in Canada, Portugal, Singapore and the United Kingdom, and the MASS Study in Spain.[5] Principal investigators from other published RCTs of children in this age group were approached to determine whether their data could be included and AEs adjudicated, but none were able to share the data due to contractual or IRB-related constraints. Both audits were covered under the original IRB approvals for the studies. The audit reviewed and documented the data listed above in all case report forms from subjects who (1) presented with any documented AEs, (2) had unscheduled visits or

(3) discontinued the study before completion. In addition a random sample of 15% of all records were reviewed for possible signs of adverse response. Each visit for these subjects was documented in an Excel spreadsheet (Microsoft, www.microsoft.com) pre-populated with response options.

The study sample size was planned around a matrix showing the MK rate and 95% confidence interval with various numbers of events and years-of-wear observed. The sample size was estimated for a single proportion in PASS 15.01.1 (NCSS Statistical Software, www.ncss.com). For example, for a study with 1-3 potential MK events, the minimum years-of-wear was 2600 to estimate a rate with a reasonable confidence interval. Without knowing the results of the adjudication process at the time of the active chart review (and therefore the final number of MK cases), subjects were included until it was estimated that this adequate number of years of lens wear had been observed.

Definitions of adverse events

Similar to other North American post-market surveillance studies of contact lenses,[17–19] the definition of MK was as follows:

"Presumed Microbial Keratitis":

1. One or more corneal stromal infiltrates >1 mm with pain >mild plus 1 or more of: anterior chamber reaction >minimal or mucopurulent discharge or positive corneal culture.
2. The presence of a subsequent corneal scar was a requirement if follow-up data and medical records were available. In the absence of data regarding resolution with a scar, aggressive treatment consistent with the standard of care for MK in North America was considered indicative (choice of medication, high frequency of dosing, etc.).

"Probable microbial keratitis" adjudication was allowed if not all of the criteria were met; for example, if the size of the lesion was less than 1 mm, the pain was minimal, there was no anterior chamber reaction, mucopurulent discharge or positive corneal culture.

All cases adjudicated as presumed or probable MK were included in the MK rate calculation. A classification of *MK unrelated to contact lens wear* was reserved for cases such as herpes simplex keratitis or *staphylococcus* marginal keratitis where, in the Adjudication Panel's judgment, the aetiology was unrelated to SCL wear. These would not be counted as MK events in the rate calculation.

Table 1 shows the definitions used for adjudication of significant AEs, including inflammatory and mechanical events. Non-significant AEs that were incorporated into this possible classification included SCL-related dryness, corneal abrasion, superficial punctate keratitis, corneal oedema, allergic conjunctivitis, bacterial conjunctivitis, episcleritis, sub-conjunctival haemorrhage and hordeolum. All adverse events were collected for review by the Panel regardless of whether they were specified as related to contact lens wear.

Table 1. Definitions for significant adverse events*

Adverse Event	Signs
Inflammatory Events:	
Contact Lens Peripheral Ulcer (CLPU) or Sterile Infiltrative Keratitis	Single, circular focal infiltrate (up to 2 mm); peripheral or mid-peripheral location; overlying corneal staining; surrounding diffuse infiltration; no anterior chamber reaction
Contact Lens Acute Red Eye (CLARE)	Diffuse infiltration in peripheral cornea; multiple small focal infiltrates; overlying corneal staining uncommon
Infiltrative Keratitis (IK)	Diffuse or small focal infiltration in anterior stroma, with overlying corneal staining
Mechanical Events:	
Contact Lens Papillary Conjunctivitis (CLPC)	Papillae on upper tarsus, localized to one region or evenly distributed across tarsus
Superior Epithelial Arcuate Lesion (SEAL)	Arc shaped, greyish white, peripheral lesion in the superior cornea. Corneal staining and surrounding diffuse infiltration
Corneal Erosion (CE)	Discrete area of full thickness loss of epithelium; may be single or multiple

*Adapted from Sweeney.[11]

Images of patient charts were electronically scanned for all visits in which a potential AE was documented, regardless of seriousness, until the AE was resolved. These included instances where biomicroscopic signs were noted at routine visits without complaints of discomfort or redness associated with SCL wear. The chart was then redacted of all personal information, site information and lens brand. Redacted records were batched and sent to the three Adjudication Panel members for independent review for diagnoses of each AE. Panel members had been chosen for their independence from the sponsor, and depth of experience as researchers or clinicians with management of complications associated with SCL wear. The Panel was not aware of the number of wearers in the dataset or the number of years observed at any point in the adjudication process. For any cases in which a unanimous diagnosis was not achieved independently, the Panel convened via telephone to discuss the AEs until they agreed to a diagnosis through a consensus process.

Data analysis

Years-of-wear were computed from the fitting date up to the last visit through 16 years of age. The annualised

incidence rate of MK was calculated by dividing the number of MK cases by the years-of-wear. A Poisson distribution was used to calculate the 95% confidence interval. The event rate for significant AEs was also calculated in a similar manner. All statistical analyses were performed using SAS software Version 9.3 (SAS Institute, www.sas.com). Non-significant AEs were tabulated and are reported, but the rate for each category was not analysed.

Results

Charts from 963 children were reviewed: 782 patients from 7 US eye care clinics and 181 subjects from two international RCTs. All of the community clinics that were approached participated by allowing access to their clinical charts. The study included 2713 years-of-wear and 4611 visits. The cohort was 46% male, 60% first fitted with daily disposable SCLs on average when 10.5 years old, with a mean observation period of 2.8 ± 1.5 years of wear. Details of enrolment in each of the community clinics are shown per site in *Table 2*. Due to different practice sizes, the unequal contribution of subjects was expected in this retrospective cohort review, but no site contributed more than 30% of the years of wear observed in the community clinics. After the completion of the active follow-up query, clinical status of 728/782 (93.1%) of the cohort was current within 9 months or less. The remaining 54/782 (6.9%) either had a clinical visit more than 9 months since completion of the chart review or did not respond to the active follow-up query. This total includes 13 (1.7%) wearers for whom we could not obtain permission from the clinical site to send an active follow-up query.

The random sample of 15% of all records in the RCT reviewed for possible signs of adverse response found no new AEs that had not been identified during the conduct of the trials.

The demographics and lens wear history of the observed cohorts in the seven community clinics and two RCTs are described in *Table 3*. Subjects from the community clinics had been fitted with a variety of lens types and wearing regimens. All of the RCT subjects wore lenses in a daily disposable (DD) regimen.

Table 3. Demographics and 1st lens details for observed cohort

	Community Clinic Patients	Randomized Clinical Trial Subjects	Total Cohort
# of Wearers N (row%)	782 (81.2%)	181 (18.8%)	963 (100%)
Sex – N (%) Male (col%)	354 (45.3%)	90 (49.7%)	444 (46.1%)
Years-of-Wear			
Total	2134.1 years	578.9 years	2713.1 years
Mean ± SD	2.7 ± 1.6 years	3.2 ± 1.4 years	2.8 ± 1.5 years
Range	0.01 to 7.6 yrs	0.02 to 5.0 yrs	0.01 to 7.6 yrs
Soft CL Design (col%)			
Single Vision Sphere	511 (65.3%)	181 (100%)*	682 (70.8%)
Toric	213 (27.2%)	-	213 (22.1%)
Multi-Focal	47 (6.0%)	-	47 (4.9%)
Unknown	11 (1.4%)	-	11 (1.1%)
Lens Replacement Schedule			
Monthly	196 (25.1)	-	196 (20.3%)
2-Weekly	165 (21.1%)	-	165 (17.1%)
Daily	401 (51.3%)	181 (100%)	582 (60.4%)
Unknown	20 (2.6%)	--	20 (2.1%)

*Or dual focus.

Age at first SCL fitting is shown in *Figure 1*. The US Census data on the racial and socio-economic demographics of the community clinic cities are shown in *Table* S2. This data is included to demonstrate our attempt to observe a diverse racial, economic and geographic sample of SCL wearers. Race and socioeconomic status were not captured in eye care clinic charts.

A unanimous agreement from the independent adjudication was reached on less than half of the diagnoses, requiring telephone discussion to reach a consensus. Conditions that were more likely to have agreement during the independent adjudication were those that presented with a clear history and succinct signs such as sub-conjunctival haemorrhage, hordeolum and corneal foreign body. Differences were often minor, e.g., conjunctivitis vs allergic conjunctivitis. Differentiating inflammatory conditions into the categories listed in *Table 1* usually required discussion.

Table 2. Details for community clinic sites

Location	Tucson, AZ	Atlanta, GA	Scranton, PA	Westerville, OH	Campbell, CA	Kirkland, WA	Carmel, IN
Practice type	Multi-OD 1 Office	Multi-OD 1 Office	Multi-OD/MD 14 Offices	Multi-OD 4 Offices	Multi-OD 1 Office	Multi-OD 2 Offices	Multi-OD 2 Offices
N	59	92	230	158	77	40	126
Yrs observed	140.8	259.0	640.7	405.3	226.5	96.4	365.4
% Years*	6.6%	12.1%	30.0%	19.0%	10.6%	4.5%	17.1%

OD, Doctor of Optometry; MD, Doctor of Medicine.
*% of Community Clinic Years.

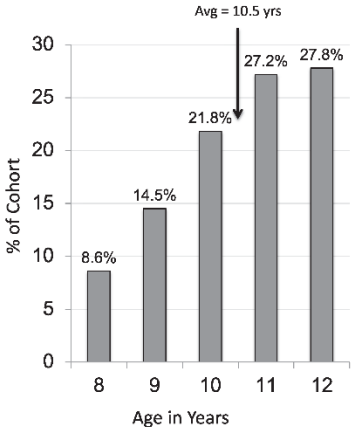


Figure 1. Age at 1st SCL Fitting N = 963.

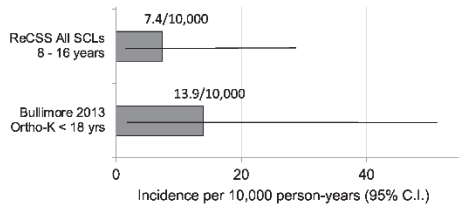


Figure 2. Comparison of annualised MK rate in ReCSS and other contact lens studies. Horizontal lines show the 95% confidence interval. 95% CI for ReCSS Study (N = 963): 1.8 to 29.6/10 000; Bullimore[19] 2013 (N = 677): 1.7–50.4/10 000.

After adjudication, two microbial keratitis (MK) cases (one presumed and one probable) were identified from the community sites; a rate of 7.4/10 000 years-of-wear (95% CI 1.8–29.6). The details of each case follow. Neither of the MK events was unanimously adjudicated as MK on the initial review by the expert Panel, but these diagnoses were reached after the Panel's independent consensus discussion. *Figure 2* shows the annualised rate of MK in children wearing soft contact lenses and the other post-market safety CL study in children utilising overnight orthokeratology lenses.[19]

The first case was considered a presumed MK in a 14-year old male who reportedly had been sleeping in his daily disposable lenses. He presented with light sensitivity and pain, a marginal ulcer in the inferior central region and no anterior chamber reaction. During an emergency room visit he was treated with ofloxacin every 30 min, then with besifloxacin every 2 h and oral ibuprofen the following day at his eye care practitioner. At resolution he had 6/6- acuity and an off-axis mild scar. During the initial adjudication round, this case was judged to be a probable MK, CLPU and MK by the three adjudicators.

The second case was a probable MK in a 13-year-old male who wore daily disposable lenses. He presented with an irritated eye that started hurting 1 day previously, and a mid-peripheral small infiltrate, trace cells and flare. He was initially treated with besifloxacin every 30 min for 2 h, and then every 2 h for the rest of that day. The following day he received one drop of homatropine, loteprednol every 8 h as well as combined loteprednol and tobramycin (Tobradex) every 2 h for 2 days, which was then tapered to every 6 h. At resolution he had 6/6 acuity and no scaring was noted. During the initial adjudication round, this case was judged to be IK, corneal infiltrate and probable MK.

Figure 3 shows the annualised rates of significant AEs observed in this study. The combined CIE events (IK, CLARE, CLPU) occurred at a combined annual rate of 0.66%/yr. *Figure 4* illustrates the age at onset for all of the MK + CIE events.

Table S3 lists the frequency of non-significant AEs and AEs that were not related to SCL wear. A wide variety of AEs was observed, most of them easily managed by temporary discontinuation of lens wear (e.g., superficial punctate keratitis, abrasion) or therapeutic management (e.g., conjunctivitis, blepharitis). The bottom of *Table* S3 lists the AEs that were not related to SCL wear; three anterior chamber AEs (Herpes Zoster, post-traumatic hyphema and a non-specific iritis with no corneal involvement) and other cases of headache and general discomfort.

Discussion

Leading researchers in this field have concluded that, "one of the major challenges for improved uptake and acceptance of contact lenses centres on the perceived risk of complications with lens wear"[20] and that "safety of all refractive correction and management options must also remain at the forefront of practitioners' recommendations".[21] The current study fills a significant gap in understanding of the safety of SCL wear specifically in children and young teens who began to use lenses before they turned 13 years of age.

This retrospective cohort study design allowed the accumulation of sufficient real-world patient experience to estimate MK with a reasonable margin of error. The age range studied aligns with the Indications for Use of the only soft contact lens currently approved for myopia control by the United States Food and Drug Administration.[7] This study of existing SCLs can be considered applicable to new myopia control soft contact lenses that use currently marketed materials with only slightly modified optics. Results from

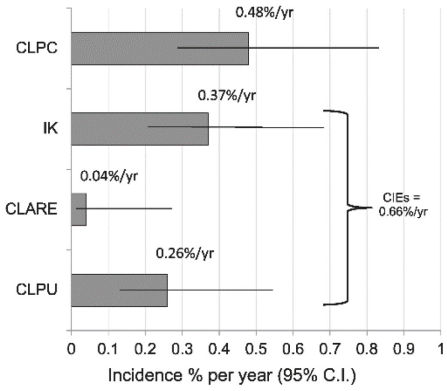


Figure 3. Annualised rate of Significant Adverse Events in the ReCSS Study. Horizontal lines show the 95% confidence interval. CLPC = contact lens papillary conjunctivitis, IK = infiltrative keratitis, CLARE = contact lens acute red eye, CLPU = contact lens peripheral ulcer.

this chart review of typical SCLs should be applicable for myopia control lenses whose myopia control function is accomplished through optical designs, but are otherwise similar in all other aspects to marketed SCLs.[1–6]

This study observed the safety outcomes in the medical charts of 782 young SCL wearers in US clinical practices and 181 subjects in two RCTs. Every effort was made to find these young wearers in a variety of clinical practice settings (size and location of practices, number of practitioners, number of locations within the practice, age of practitioners, etc.). The children were observed for an average of 2.8 years and up to 7.6 years for a total of 2713 wearer-years. In comparison, the largest previous effort to study AEs in young SCL wearers, the CLAY 2011 study, had only 243 wearers and approximately 200 years-of-wear in the 8–12 year old age group; that was appropriate to find overall AE rates but was too small to estimate an annualized rate of MK.[14] The 2013 post-market surveillance study by Bullimore et al reported on 1145 years of wear in minors up to age 18, but the proportion fitted before age 13 was not noted.[19] *Figure 2* shows the rate of MK in that clinical trial relative to the current study. Additionally, in a 2017 review of serious AEs in children wearing SCLs, Bullimore found that there were no MK events reported among minors in any of the prospective clinical trials reviewed (over 1800 years of wear).[20]

Figure 5 shows the annualised rates of all CIEs + MK combined in this study with the CLAY study cohort by age group.[10]

Clinical trials of the efficacy of myopia control soft contact lenses have been designed to test the effect of lens wear on refractive error, and are typically in the range of 200 subjects followed longitudinally for at least 2 years.[21,22] This retrospective cohort study design allowed us to follow this large diverse cohort of young wearers fitted by many practitioners in practice. The observed follow-up times ranged from a few days (for a small number of subjects that discontinued early in the RCT) to over seven years.

Weaknesses in the retrospective cohort approach include the inability to balance the age at first fitting across the age group from 8–12 year olds. An observational study can only examine those patients who were actually prescribed

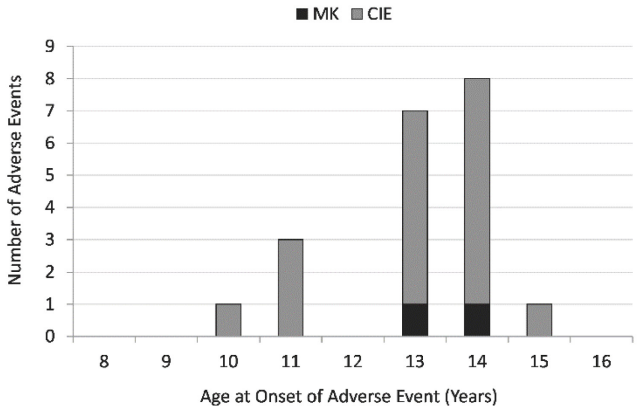


Figure 4. Corneal infiltrative and microbial keratitis events observed by age of onset in ReCSS Study. N = 963.

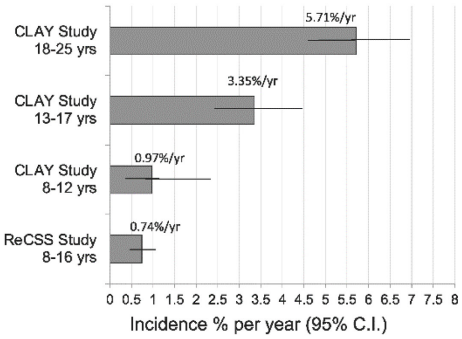


Figure 5. Comparison of annualised rate of Significant Inflammatory Events (All CIEs + MK) in ReCSS and the CLAY study[14] by age group. Horizontal lines show the 95% confidence interval. Sample sizes: CLAY Study[14] 18–25 years N = 1129; 13–17 years N = 811; 8–12 N = 243, ReCSS Study 8 16 years N = 963.

and wearing the SCLs under investigation. Also, due to the unknown number of young SCL patients that would be identified in each practice, the sequential review yielded unequal numbers of wearers at each site, because there were different numbers of SCL-wearing children in those practices. Unequal sample sizes between sites is typical in observational studies. There were no more than 30% of the years of wear observed in any one practice. Additionally, in this type of study, without a concurrent questionnaire at the time of the events regarding how SCLs were being used (overnight wear, swimming, etc.) it is not possible to study risk factors for the AEs that were observed.

Most professional organisations recommend at least annual visits for children and SCL wearers.[23] One strength of the study was the addition of an active follow-up step for any children who were still wearing lenses but had not been seen by the practice in the past nine months, which we were able to do in five of the seven community clinic sites. This outreach step resulted in only a small percentage (6.9%) of subjects who either did not respond with their current disposition or had not been examined in nine months, an acceptable rate for a retrospective cohort study.[24]

The annualized rate of MK in this study, 7.4/10 000 years-of-wear, was computed from two cases; one "presumed" and one "probable" case. This rate is slightly lower, but not significantly different, from the MK rate from the other post-market study with overnight orthokeratology CLs in children shown in *Figure 2*.[19] The current study provides a lower rate and tighter confidence interval than other paediatric post-market studies, which may offer reassurance to clinicians who are counselling parents of young children regarding the safety of myopia control soft contact lenses. The rate is also comparable to established rates of MK in adults, from 1–4/10 000 for adults with daily wear hydrogel lenses[18] and 18-20/10 000 for overnight wear of silicone hydrogel lenses.[10,17,18]

It is notable that the two MK events occurred in young teens aged 13 and 14 years old from community practices, one of whom reported overnight wear of his DD SCLs. During the adjudication process, these AEs were not unanimously judged as MK cases by all three experts but were discussed by the panel to reach that consensus diagnosis. This lack of early agreement on the diagnosis amongst the panel reflects the relatively mild severity and positive outcomes that did not affect visual acuity in either case. Most of the CIEs occurred in this age range as well.

The current results were observed in patients using purchased lenses in the "real world" and not exclusively in RCTs where lenses are often supplied for free. The authors assume that there were examples of non-compliance of SCL-related behaviours in this age group as in adults; some patients sleeping while wearing SCLs or wearing them while swimming, etc.[25] In fact, these young wearers may be more compliant, as the CLAY Study team, using a validated contact lens risk questionnaire, found that CL compliance was related to age, with the youngest group showing the highest level of compliance.[26] The patients' young age does give the eye care practitioner the opportunity to engage parents as additional support for supervision of compliant lens wear. A rigorous programme of training and retraining on the best practices for safe SCL use that is engaging to young wearers will be important to the long-term safety and success of myopia control soft contact lenses as a management option for myopia.

When combining MK plus other inflammatory AEs in this age group, the annualised rate was 0.74%/yr, which compares very well with the 0.97%/yr and 3.35%/yr reported in the CLAY study groups that were between 8–12 and 13–17 years old respectively (*Figure 5*).[14] The CLAY study was selected for comparison because it included a similar retrospective chart review study design, and had a substantial number of wearers who were fitted while they were 8–12 years old and reported events by age groups when they experienced an AE. The current findings are very similar to but slightly lower than rates from the two youngest age groups reported in the CLAY study, as shown in *Figure 5*. This could be attributed to the fact that the current study had a much higher proportion of DD lens use compared with the CLAY study (8–12 year olds; 60.8% vs 15.8%).[12] This may explain the lower rate in the current study as the use of DD lenses is associated with a reduced rate of inflammatory events.[14,25-27] Inflammatory AEs are of special interest as they typically require pharmaceutical management and differential diagnosis with MK to assure there is no risk of vision loss.

The summary of non-significant AEs experienced by these young wearers shows a relatively high rate of conjunctivitis (19 cases) and abrasion/foreign body events (14 cases), which seem reasonable in a sample of school aged children. These AE results show the safety outcomes primarily derived from routine eye care practice visits and not exclusively from clinical trials with frequent defined visits; most of these youngsters received eye examinations approximately annually, and only presented for interim visits when they experienced problems. Compared to safety results derived exclusively from clinical trials, these results are likely to be more generalizable to the post-market experience after myopia control soft contact lenses are prescribed more widely to young patients in practice.

These results give assurance of an acceptable range of safety during SCL wear in children which will be reinforced with teaching protocols that emphasise best practices for safe SCL wear. Much of the safety discussion amongst myopia control researchers promotes the potential long-term safety implications of reduced retinal disease and other sight-threatening ocular abnormalities if higher levels of myopia can be avoided;[20,22] although it may be difficult for families and eye care practitioners to imagine that far into the future. The results of the current study help to answer parents' and practitioners' concerns about the risk/benefit of real-world SCL use in children and young teens and assure the relative safety of SCL use in this age group.

Acknowledgements

This study was funded by CooperVision, Inc. We thank all the eye care practitioners listed in *Table* S1 for their cooperation with the study. Members of the Adjudication Panel were Thomas G. Quinn, OD, MS, FAAO, Dip (CCLRT) in private practice in Athens, OH; Oliver D. Schein, MD, MPH of Johns Hopkins University Bloomberg School of Public Health in Baltimore, MD; and Loretta Szczotka-Flynn, OD, PhD, FAAO, Dip(CCLRT) of Case Western Reserve University in Cleveland, OH. Regulatory assistance was provided by Foresight Regulatory Strategies, Inc. Access to the RCT's was facilitated by the staff of VisionCare Research, Inc of Farnham, Surrey, UK and the European University of Madrid School of Optometry. Data management assistance was provided by Julia Fulmer, Corrin Lesjak, Rebecca Purser, Nathan Sinyangwe, Cheryl Taylor and Ross Wofford.

Author contribution

Robin L Chalmers: Conceptualization (equal); Data curation (lead); Investigation (lead); Methodology (equal); Project administration (lead); Writing-original draft (lead); Writing-review & editing (equal). **John J McNally:** Conceptualization (equal); Funding acquisition (lead); Methodology (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Paul Chamberlain:** Conceptualization (equal); Funding acquisition (lead); Investigation (supporting); Methodology (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Lisa Keay:** Formal analysis (equal); Methodology (equal); Writing-original draft (supporting); Writing-review & editing (supporting).

Disclosures

Robin Chalmers is a consultant for AcuFocus Inc., Alcon Research, Ltd., CooperVision Inc., Johnson & Johnson Vision, Inc., and Vision Service Plan, Inc. John McNally and Paul Chamberlain are employees of CooperVision, Inc. Lisa Keay is a consultant for CooperVision, Inc.

References

1. Anstice N & Phillips J. Effect of dual-focus soft contact lenses on axial myopia progression in children. *Ophthalmology* 2011; 118: 1152–1161.
2. Walline JJ, Greiner KL, McVey KL & Jones-Jordan LA. Multifocal contact lens myopia control. *Optom Vis Sci* 2013; 90: 1207–1214.
3. Aller TA & Wildsoet C. Myopia control with bifocal soft contact lenses: a randomized clinical trial. *Optom Vis Sci* 2016; 93: 344–352.
4. Chamberlain P, Back A, Lazon P *et al.* A 3-year randomized clinical trial of MiSight lenses for myopia control. *Optom Vis Sci* 2019; 96: 556–567.
5. Ruiz-Pomeda A, Perez-Sanchez B, Valls I, Prieto-Garrido FL, Gutiérrez-Ortega R & Villa-Collar C. MiSight Assessment Study Spain (MASS). A 2-year randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2018; 256: 1011–1021.
6. Sankaridurg P, Bakaraju RC, Naduvilath T *et al.* Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. *Ophthalmic Physiol Opt* 2019; 39: 294–307.
7. https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180035A.pdf.
8. Wolffsohn JS, Calossi A, Cho P *et al.* Global trends in myopia management attitudes and strategies in clinical practice – 2019 update. *Cont Lens Anterior Eye* 2020; 43: 9–17. Epub 2019 Nov 21. https://pubmed.ncbi.nlm.nih.gov/31761738/?from_term=Wolffsohn%2C+contact+lens&from_page=5&from_pos=8#affiliation-5
9. Sindt CW & Riley CM. Practitioner attitudes on children and contact lenses. *Optometry* 2011; 82: 44–51.
10. Stapleton F, Keay L, Edwards K *et al.* The incidence of contact lens related microbial keratitis. *Opthalmology* 2008; 115: 1655–1662.

11. Sweeney DF, Jalbert I, Covey M *et al.* Clinical characterization of corneal infiltrative events observed with soft contact lens wear. *Cornea* 2003; 22: 435–442.
12. Lam DY, Kinoshita BT, Jansen ME *et al.* Contact lens assessment in youth: methods and baseline findings. *Optom Vis Sci* 2011; 88: 708–715.
13. Wagner H, Chalmers R, Mitchell L *et al.* Risk factors for interruption to soft contact lens wear in children and young adults. *Optom Vis Sci* 2011; 88: 973–980.
14. Chalmers RL, Wagner H, Mitchell GL *et al.* Age and other risk factors for corneal infiltrative and inflammatory events in young soft contact lens wearers from the contact lens assessment in youth (CLAY) study. *Invest Ophthalmol Vis Sci* 2011; 52: 6690–6696.
15. Chalmers RL, Keay L, Long B, Bergenske P, Giles T & Bullimore MA. Risk factors for contact lens complications in US clinical practices. *Optom Vis Sci* 2010; 87: 725–735.
16. Use of Real-World Evidence to Support Decision-Making for Medical Devices. *Guidance for Industry and Food and Drug Administration Staff.* Issued August 31, 2017. (https://www.fda.gov/news-events/fda-brief/fda-brief-fda-issues-new-guidance-facilitate-expanded-use-real-world-evidence).
17. Schein OD, McNally JJ, Katz J *et al.* The Incidence Of Microbial Keratitis among wearers of a 30-day silicone hydrogel extended-wear contact lens. *Ophthalmology* 2005; 112: 2172–2179.
18. Poggio EC, Glynn RJ, Schein OD *et al.* The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. *N Engl J Med* 1989; 321: 779–783.
19. Bullimore MA, Sinnott LT & Jones-Jordan LA. The risk of microbial keratitis with overnight corneal reshaping lenses. *Optom Vis Sci* 2013; 90: 937–944.
20. Bullimore MA. Safety of soft contact lenses in children. *Optom Vis Sci* 2017; 94: 638–646.
21. Sankaridurg P. Contact lenses to slow progression of myopia. *Clin Exp Optom* 2017; 100: 432–437.
22. Bullimore MA & Richdale K. Myopia control 2020: where are we and where are we heading? *Ophthal Physio Opt* 2020; 40: 254–270.
23. https://www.aoa.org/patients-and-public/caring-for-your-vision/comprehensive-eye-and-vision-examination/recommended-examination-frequency-for-pediatric-patients-and-adults. Accessed on June 15, 2020.
24. Kristman V, Manno M & Côté P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol* 2004; 19: 751–760.
25. Chalmers RL, Hickson-Curran SB, Keay L, Gleason WJ & Albright R. Rates of adverse events with hydrogel and silicone hydrogel daily disposable lenses in a large postmarket surveillance registry: the TEMPO Registry. *Invest Ophthalmol Vis Sci* 2015; 56: 654–663.
26. Wagner H, Richdale K, Mitchell GL *et al.* Age, behavior, environment, and health factors in the soft contact lens risk survey. *Optom Vis Sci* 2014; 91: 252–261.
27. Chalmers RL, Keay L, McNally J & Kern J. Multicenter case-control study of the role of lens materials and care products on the development of corneal infiltrates. *Optom Vis Sci* 2012; 89: 316–325.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Clinical Trial Sites & Investigators
Table S2 US Census data for community clinic cities
Table S3 Non-significant adverse events (AEs) and events not related to soft contact lens wear

CHAPTER 6: CONSIDERATIONS FOR THE ASSESSMENT OF EFFICACY

6.1. Exploring further quantifications of efficacy across the 6-year trial

The 6-year clinical trial of the MiSight contact lens indicated that hydrogel myopia control contact lenses could be worn safely by children on a full-time basis over many years. The evidence detailed in Chapter 4 also provided support for continued slowed eye growth for the original treated group as well as slowed growth and progression in the original control group who began treatment during the second three-year study period. However, due to the lack of a concurrent matched control group during the second three-year phase, efficacy was assessed less rigorously using comparative analyses between treated and untreated populations over different phases of the study. For example, efficacy estimates were derived by comparing untreated progression (T3 group) in the first three years (Years 1-3) with treated progression for the same population in the subsequent three years (Years 4-6). Efficacy was also implied for the continuing treatment group (T6) by comparing growth and progression during treated years 4-6 with that observed during years 1-3, and also by comparing T6 results with the newly treated T3 group during the second three-year period. While informative, such methods are inherently limited by the absence of concurrent matched untreated control data.

One of the primary challenges in efficacy assessment is the inherent variability in myopia progression due to demographic and environmental factors. For instance, race, gender, geographic location, and even seasonal variations significantly influence untreated myopia progression. (Goss and Rainey 1998, Fulk, Cyert et al. 2002, Donovan, Sankaridurg et al. 2012, Gwiazda, Deng et al. 2014) The general slowing of myopia progression with age further complicates efforts to isolate treatment effects within a cohort and complicates comparison between studies. (Jones, Mitchell et al. 2005, Chua, Sabanayagam et al. 2016) These age and environmental effects are likely contributors to the reported high variability over time in growth and progression of myopic eyes which complicates efficacy assessment from comparisons of pre-treatment and during treatment growth and progression. (Mutti, Sinnott et al. 2022)

Projections of long-term myopia control treatment efficacy are crucial for contextualizing myopia control within broader healthcare objectives such as reducing risk of future eye disease (Flitcroft 2012) given the correlation of myopia level to risk of eye disease. (Bullimore and Brennan 2019) The link to future eye disease prevention also enables an estimation of the cost vs. benefit of these interventions on health systems, (Fricke, Sankaridurg et al. 2023, So, Lian et al. 2024) which may play an important role when government consider investment and/or promotion of infrastructure to support myopia control interventions. These projections were uncertain because many clinical studies of myopia control are short term (Lawrenson, Shah et al. 2023) with data collected for only one or two years and many of these studies exhibit a reduction in efficacy after the first year. (Brennan and Cheng 2019, Brennan, Toubouti et al. 2020) Reductions in efficacy defined by absolute mm or diopters were also observed in the MiSight Trial (Chapter 3). This raises the important question of whether myopia control interventions can be sustained over the extended periods, which can exceed 10 years, during which the myopia continues to progress? (Hardy, Hillis et al. 2013, Qin, Peng et al. 2022)

In addition to the inherent challenges of long-term clinical trials, maintaining untreated control groups over long periods poses ethical dilemmas, as discussed in Chapter 4, particularly as myopia control treatments become more widely available. In the MiSight trial and similar studies, untreated groups were transitioned to treatment after the initial phase or discontinued, limiting the ability to measure long-term efficacy against a concurrent control group. (Lam, Tang et al. 2023, Ll, Huang et al. 2024, Berntsen, Tićak et al. 2025) High dropout rates in control groups, driven by parental reluctance to withhold treatment, exacerbate this issue. (Arumugam, Bradley et al. 2024) Therefore, although regulatory pressures and clinical

trial rigor prioritize a concurrent control group, after efficacy had been established for MiSight (Chapter 3), continuing the untreated control group would be an example of denial of treatment.

In the next two chapters, the precise axial length measurements collected during the 6-year MiSight clinical trial are utilized to explore novel approaches to evaluate myopia control efficacy given that long term treatment efficacy will not be able to be assessed by comparing treated to concurrent randomized and masked untreated control groups. Axial length measured with an optical biometer (IOL Master, Zeiss) has proven repeatability (95% limits of agreement (LOA) of -0.047 to +0.039. (Lam, Chan et al. 2001) The IOL Master LOA is equivalent to a dioptric value of -0.09 to 0.08 diopters which contrast to the less precise (more variable) LOA of spherical refractions between -0.36 to +0.40 and between -0.9 to 0.65 diopters, respectively for automated and subjective refractions. (Bullimore, Fusaro et al. 1998) These results suggest that myopia progression may be more precisely monitored using optical biometry. (Brennan, Toubouti et al. 2020)

6.2. Efficacy in the context of emmetropic eye growth

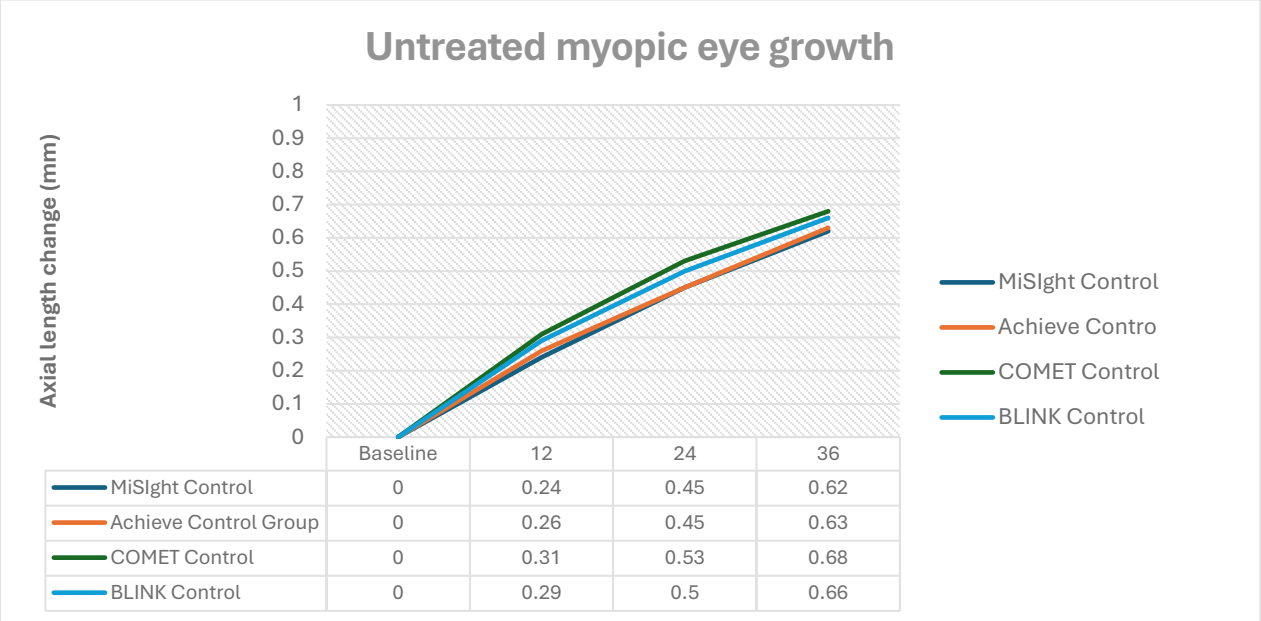
A pertinent question in myopia control is what is the maximum achievable efficacy? Theoretical scenarios where 100% efficacy is attained by stopping axial elongation in treated populations (average growth equal to zero for multiple years) implies a regression in axial length for half of that population. This seemingly implausible outcome is compounded when there is evidence of continued axial elongation throughout childhood and into teenage years for non-myopic eyes. (Zadnik, Mutti et al. 2004, Mutti, Sinnott et al. 2023, Rozema, Dankert et al. 2023)

Given that emmetropic eye growth does not impact refractive stability, it is often termed as “physiological eye growth” or more accurately, fully “compensated eye growth”.(Mutti, Sinnott et al. 2023) This occurs as a result of matched increases in the optical length (focal plane location) and anatomic length (retinal plane location). Because corneal power stabilizes at an early age, (Mutti, Sinnott et al. 2018) it is likely that crystalline lens position and power changes are responsible for the overall reduction in optical power as the eye grows during childhood and adolescence. (Zadnik, Mutti et al. 2004, Mutti, Sinnott et al. 2018, Rozema, Dankert et al. 2019)

The Orinda Longitudinal Study of Myopia (OLSM) tracked axial growth of emmetropic children with at least 2 years of follow up data between the ages of 6 and 14 years old.(Zadnik, Mutti et al. 2004) Inspection of the axial length of emmetropic eyes of children between 8 and 15, mirroring the ages of the MiSight trial participants, reveals average annual axial length increases of approximately 0.15mm at age 8, declining gradually to level less than 0.1mm between ages 12-14. This finding was further supported by the larger data set collected in the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study, a follow-on study from OLSM which expanded sites to explore ethnic differences in myopia progression and eye growth.(Mutti, Hayes et al. 2007) The average axial elongation of 0.1mm per year observed in the CLEERE emmetropic populations between 10 and 13 closely mirrors the axial growth rate observed in the MiSight treated population (Chapter 3). (Mutti, Hayes et al. 2007) The similarity of axial growths of MiSight treated eyes and emmetropic eyes of the same age led to the hypothesis that MiSight therapy returned eye growth in progressing myopic eyes to physiological eye growth. A further publication from the OLSM study provided equations to predict eye growth for both emmetropes and myopes for a given age, allowing estimates of average growth for a population of age-matched emmetropic eyes (Jones, Mitchell et al. 2005) to be compared directly with the average growth observed in the MiSight treated eyes. (Chamberlain, Peixoto-de-Matos et al. 2019) Similarly, the replicate study of ocular component changes in Singapore, provided growth curves for emmetropic Asian eyes.(Wong, Machin et al. 2010) The publications in this chapter compared annual axial growth in MiSight treated eyes to expected growth of age-and race-matched emmetropic eyes via these models.

6.3. Exploring alternatives to concurrent control groups for quantifying efficacy

When seeking FDA approval for the MiSight lens, the agency expressed concern that the studied population was not representative of myopia progression in the United States, and related to this, a concern that any efficacy measure would also not be representative of that population. At that time, data from three US based studies reported untreated myopia progression in children corrected with either single focus contact lenses or spectacles. (Gwiazda, Hyman et al. 2003, Walline, Jones et al. 2008, Walline, Walker et al. 2020) The average age of the studied US populations at study initiation ranged from 9.4 to 10.5 years old, close to the MiSight study average of 10.1 years. Each study explored myopia progression for 3 years. Although axial length measurements are more repeatable, (Brennan, Toubouti et al. 2020) they are not a direct measure of myopia progression because some of the axial growth of myopic eyes can be considered normal "compensated" or non-myopia generating eye growth. (Mutti, Sinnott et al. 2023) However, high precision optical biometry provides a precise way to compare growth of untreated myopic eyes, with myopic eyes undergoing myopia control therapy and with emmetropic eyes. Figure 10 details the 3-year axial elongation of untreated myopic eyes over a 3-year period measured in 4 studies, including the MiSight trial. Despite these trials being conducted across a 20-year period with slightly different ages, they show remarkable consistency in average 3-year axial elongations.



	Baseline	12	24	36
MiSIght Control	0	0.24	0.45	0.62
Achieve Control Group	0	0.26	0.45	0.63
COMET Control	0	0.31	0.53	0.68
BLINK Control	0	0.29	0.5	0.66

Figure 10: Axial length growth of young myopic eyes recorded at 12, 24, and 36 months after a baseline measure are plotted for 4 different studies: Control group from the MiSight trial and the Blink, COMET and Achieve studies in the US.

The consistency observed in untreated myopia progression data suggests that historical axial growth data could be used to predict future eye growth of myopic eyes. This approach allows researchers to make reliable projections about the expected progression of untreated myopic eyes. To achieve this, predictive models have been developed that utilize historical progression data to estimate future trends. A meta-analysis examining axial elongation in progressing myopic eyes across multiple global populations found that annual growth rates followed an exponentially slowing trajectory.(Brennan, Shamp et al. 2024) Notably, the study reported that Asian eyes exhibited a 38% higher growth rate compared to non-Asian eyes, a

pattern that aligns with numerous studies documenting differences in myopia progression in Asian cohorts versus non-Asian cohorts.

Due to the wide variation observed annual growth rates between and within study populations, it is not recommended to simply create a ‘virtual control group’ using only mean baseline age and racial mix of a baseline population, but rather, use existing untreated data in the study cohort and then apply the average 15% per year slowing rule to the measured axial elongation. (Brennan, Shamp et al. 2024) This approach was used to predict the expected axial lengths of the original control eyes in the MiSight trial if they had remained untreated for the second three-year phase of the 6-year study. The applicability of the 15% slowing per year rule to the study cohort was confirmed for the MiSight untreated control cohort by comparing untreated growth in Years 2 & 3 relative to that observed in year 1. This "virtual control group" approach has since been utilized in multiple studies and provides a framework for quantifying long-term efficacy. (Bullimore and Brennan 2023, LI, Huang et al. 2024)

In the two publications of this chapter, we examined different strategies to assess myopia control efficacy when no concurrent randomized control group was available. First, using historical axial growth data in emmetropic eyes, eye growth was compared in MiSight treated eyes to that observed in emmetropic eyes and test the hypothesis that MiSight treatment slowed the accelerated eye growth that underlies myopia progression to that observed in non-myopic eyes. (Chamberlain, Jara et al. 2021, Chamberlain, Hammond et al. 2024) Historical growth data observed in untreated myopic eyes was used to predict the axial growth of the initial control eyes as if they had remained untreated. These “virtual” controls were used as would be a concurrent study control to assess treatment efficacy by the amount of slowing created by treatment. We also employed an approach to assess treatment efficacy based upon time, not mm or diopters, which did not require the control group to be maintained for the full 6 years of the extended clinical trial. With this approach we assess how long it took treated eyes of individuals and the cohort means to reach levels observed in those untreated control eyes during years 1-3 of the study.

6.4. Publication: Axial length targets for myopia control

OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS

Ophthalmic and Physiological Optics ISSN 0275-5408

Axial length targets for myopia control

Paul Chamberlain[1], Percy Lazon de la Jara[1], Baskar Arumugam[1] and Mark A Bullimore[2]

[1]CooperVision Inc., Pleasanton, USA, and [2]College of Optometry, University of Houston, Houston, USA

Citation information: Chamberlain P, Lazon de la Jara P, Arumugam B, & Bullimore MA. Axial length targets for myopia control. *Ophthalmic Physiol Opt*. 2021. https://doi.org/10.1111/opo.12812

Keywords: axial length, children, contact lenses, myopia, myopia control

Correspondence: Paul Chamberlain
E-mail address:
PChamberlain@coopervision.com

Received: 14 November 2020; Accepted: 8 February 2021

Presented in part at the 16th Biennial International Myopia Conference (IMC) in Birmingham, September 2017.

Abstract

Purpose: Both emmetropic and myopic eyes elongate throughout childhood. The goals of this study were to compare axial elongation among untreated progressing myopes, progressing myopes treated with a myopia control contact lens and emmetropes, in order to place axial elongation in the context of normal eye growth in emmetropic children, and to consider whether normal physiological eye growth places limits on what might be achieved with myopia control.

Methods: Axial elongation data were taken from the 3-year randomised clinical trial of a myopia control dual-focus (MiSight® 1 day) contact lens. These were compared with data for myopic and emmetropic children in two large cohort studies: the Orinda Longitudinal Study of Myopia (OLSM) and the Singapore Cohort Study of the Risk Factors for Myopia (SCORM). Each study's published equations were used to calculate annual axial elongation. Four virtual cohorts—myopic and emmetropic for each model—were created, each with the same age distribution as the MiSight clinical trial subjects and the predicted cumulative elongation calculated at years 1, 2 and 3 for myopes and emmetropes using both the OLSM and SCORM models.

Results: The untreated control myopes in the MiSight clinical trial showed mean axial elongation over 3 years (0.62 mm) similar to the virtual cohorts based on the OLSM (0.70 mm) and SCORM (0.65 mm) models. The predicted 3-year axial elongation for the virtual cohorts of emmetropes was 0.24 mm for both the OLSM and SCORM models—similar to the mean 3-year elongation in MiSight-treated myopes (0.30 mm).

Conclusions: The 3-year elongation in MiSight-treated myopes approached that of virtual cohorts of emmetropes with the same age distribution. It is hypothesised that myopic axial elongation is superimposed on an underlying physiological axial elongation observed in emmetropic eyes, which reflects increases in body stature. We speculate that optically based myopia control treatments may minimise the myopic axial elongation but retain the underlying physiological elongation observed in emmetropic eyes.

Introduction

Myopia is quantified by the dioptric distance of the eye's far point. This definition of myopia has important historical value in that it specifies the power of the optical lens required to correct it, but it belies the fact that the primary origin of the majority of myopia does not lie with the optical components of the anterior eye, but rather in excessive axial elongation of the globe. Indeed, the distribution of corneal power among different refractive groups is very similar.[1] Although axial length is highly correlated with adult spherical refractive error,[2] a large range of axial lengths are observed for any single refractive error,[1] indicating that axial length is not uniquely associated with spherical equivalent refractive errors and eye size differences can exist without generating myopia. Larger emmetropic adult eyes also have longer focal lengths due to larger radii of the cornea and lens, with increasing lens radii (surface flattening) playing the major role in maintaining emmetropia.[3] Furthermore, the relationship between axial length and

refractive error may be nonlinear and vary with age, eye size or both.[4,5]

The eye and its components grow from birth through childhood. Corneal power reaches an average power of 43 to 44 D by 9 months of age and remains stable throughout early[6] and later childhood.[7] In contrast, all eyes elongate steadily throughout childhood.[8] Vitreous chamber depth is the largest single component of overall axial length, which elongates from an average of 12 mm at 3 months[6,9] to a final average value of around 16 mm in emmetropic eyes.[7] The rate and time course of axial elongation and ultimate axial length varies across refractive groups.[8,10,11] In myopes, axial length follows a similar rate of growth to emmetropes up to a few years before myopia onset.[8] Thereafter, at the ages when axial elongation is steadily slowing in emmetropes it continues, and even accelerates.[8,11] Indeed, the peak rate of axial elongation occurs in the 2 to 3 years before myopia onset.[8] Refractive error changes are larger before, as well as after, the onset of myopia compared to eyes that remain emmetropic.[8] Thereafter, the rate of myopia progression[12] and axial elongation[13] decreases steadily, likely following an exponential decay.[13,14] The crystalline lens undergoes age-related flattening from birth to 10-12 years of age,[7,15,16] although lens power decreases beyond this age.[7,15] Power changes of the lens compensate for ongoing axial elongation, which maintains emmetropia. Although the lens flattens at a higher rate in myopic eyes, it is insufficient to compensate for the more rapid axial elongation.[11,16,17]

In a recent summary report, the increased precision of axial length measurements, combined with the observation that future pathologies in highly myopic eyes are associated with excessive axial elongation of young eyes, prompted a conclusion that, "the goal of all clinical trials for myopia control should be the reduction of axial elongation."[18] Indeed, increasing levels of myopia are strongly associated with a range of diseases,[19,20] including myopic maculopathy,[21] open angle glaucoma,[22] posterior subcapsular cataract[23] and retinal detachment.[24] Furthermore, visual impairment is more strongly associated with axial length than refractive error.[25] It is not surprising, therefore, that axial elongation has become an important outcome measure in clinical trials of interventions to slow the progression of myopia.[18,26] Most,[27,28] though not all,[29,30] widely adopted interventions show concurrent slowing of myopia progression and axial elongation. Three-year clinical trials of myopia control are rare,[31-33] but the MiSight® 1 day dual-focus soft contact lens demonstrates a slowing of axial elongation across all 3 years of treatment[34] and 6-year findings have been presented recently.[35]

Myopia routinely develops between the ages of 5 and 15 years,[36] and therefore its time course overlaps that of the coordinated eye growth that results in and maintains emmetropia. This raises the issue of whether the increases in axial length among children with progressing myopia reflect only abnormal myopic elongation, or some combination of normal and abnormal eye growth. Here, the trajectory of axial elongation in treated and untreated myopic eyes are compared with published models of eye growth in progressing myopes and emmetropes.[7,37] The goals of the analysis were:

- To compare eye growth, in terms of axial elongation among untreated progressing myopes, treated progressing myopes and emmetropes;
- To place the axial elongation in treated and untreated myopes in the context of normal eye growth in emmetropic children;
- To consider whether normal physiological eye growth places limits on what might be achieved in myopia control.

Methods

The current study analysed axial elongation data obtained during a 3-year randomised controlled clinical trial of a myopia control dual-focus contact lens (MiSight® 1 day).[34] In brief, the study enrolled 144 myopic children aged 8 to 12 years with no prior contact lens experience in a 3-year, double-masked, randomised clinical trial at four investigational sites in Canada, England, Portugal and Singapore. Around half of the participants were of European descent and a quarter were East Asian. Subjects with −0.75 to −4.00 D of myopia and <1.00 D of astigmatism were randomised to either a MiSight contact lens (treated) or Proclear® 1 day single vision lens (untreated), both manufactured in omafilcon A (CooperVision, Inc., coopervision.com) and worn on a daily disposable basis. Compliance was high, with mean reported wearing time at the end of the study over 13 hours per weekday and over 12 hours per weekend day. Primary outcome measures were cycloplegic auto-refraction measured using the Grand Seiko Binocular Auto-refractor/ Keratometer WR-5100K or WAM-5500 (Grand Seiko Co., grandseiko.com) and axial length measured using the IOLMaster (Carl Zeiss Meditec, zeiss.com). Of the subjects who were dispensed lenses, 81% (109/135) completed the 3-year clinical trial (53 treated, 56 untreated). Unadjusted mean myopia progression was 0.73 D lower in the treated group than the untreated group (−0.51 ± 0.64 D vs −1.24 ± 0.61 D, $p < 0.001$). Mean axial elongation was 0.32 mm less in the treated group than the untreated group (0.30 − 0.27 vs 0.62 − 0.30 mm, $p < 0.001$). Changes in refractive error and axial length were highly correlated ($r = -0.90$, $p < 0.001$).

The above longitudinal axial length data were compared with data for myopic and emmetropic children in two large cohort studies: the Orinda Longitudinal Study of Myopia (OLSM) in the United States[38] and the Singapore Cohort Study of the Risk Factors for Myopia (SCORM).[39] Both

studies used cycloplegic auto-refraction for refractive error and contact ultrasound for axial length and have published equations for the growth of ocular components in children.[7,37]

The OLSM included children between 6 and 14 years of age who were required to attend at least three annual visits to be included in the analysis. Of the 1504 children recruited, 737 were eligible for the analysis. Of these, 247 children were classified as myopic (178 white and 59 Asian, with at least –0.75 D in both meridians), of whom 76% were emmetropic or hyperopic at baseline, and 194 persistent emmetropes (170 white and 16 Asian).[7] SCORM included children aged between 6 and 12 years and, again, at least three visits were required to be eligible for the analysis. Of the 1979 children recruited, 1775 were eligible of whom 616 were progressing myopes (at least –0.50 D spherical equivalent) and 369 were emmetropes. This population was predominantly Chinese in ethnicity.[37]

The OLSM and SCORM published equations for axial length[7,37] that were used to compare with the MiSight clinical trial data. The OLSM paper presents two separate equations for children younger or older than 10.5 years.[7] The SCORM paper presents a quadratic model for axial elongation fitted for ages up to 12 years.[37] Unfortunately, their model asymptotes at age 13 years and thereafter predicts shrinking of eye length. Given that comparisons were to be made for children through the age of 15 years, their equations for vitreous chamber depth, which do not suffer from the same limitations, were substituted. Their reported longitudinal changes in anterior chamber depth and lens thickness cancel each other, so vitreous chamber depth is a reasonable surrogate for axial length.

In summary, the following equations as a function of age were used.

OLSM [7]:

Myopes up to 10.5 years:

$$\text{Axial Length} = 18.144 + 2.391\ln(\text{age}).$$

Myopes after 10.5 years:

$$\text{Axial Length} - 17.808 - 2.560\ln(\text{age}).$$

Emmetropes up to 10.5 years:

$$\text{Axial Length} = 20.189 - 1.258\ln(\text{age}).$$

Emmetropes after 10.5 years:

$$\text{Axial Length} = 21.353 - 0.759\ln(\text{age}).$$

SCORM [37]:

Myopes:

$$\text{Vitreous Chamber Depth} = 20.83 - 29.811\ \text{age}^{-1} - 0.025\ \text{age}.$$

Emmetropes:

$$\text{Vitreous Chamber Depth} = 17.18 - 10.045\ \text{age}^{-1}.$$

ln = natural logarithm.

Using the above equations, axial lengths (or vitreous chamber depth) at ages 8 through 15 years were calculated. Thereafter, annual elongation was calculated.

Finally, four virtual cohorts were created, each with the same age distribution as the MiSight clinical trial subjects at baseline: 14% of 8 year olds, 27% of 9 year olds, 16% of 10 year olds, 23% of 11 year olds and 20% of 12 year olds (mean = 10.1 years). The predicted elongation was calculated at years 1, 2 and 3 for myopes and emmetropes using both the OLSM and SCORM models.

Results

Table 1 shows the annual axial elongation rates (mm/year) predicted by the OLSM and SCORM models in myopes and emmetropes. As expected, annual axial elongation is higher in myopes than in emmetropes, and annual axial elongation decreases with age.

Table 2 and *Figure* 1 show the observed cumulative axial elongation at years 1, 2 and 3 of the MiSight clinical trial for both treated and control groups. Also shown are elongation rates for myopes and emmetropes as predicted using both the OLSM and SCORM models for virtual cohorts.

The untreated control myopes in the MiSight clinical trial show similar cumulative axial elongation over 3 years

Table 1. Annual axial elongation (mm/year) as a function of age predicted by the OLSM[7] and SCORM[37] models in myopes and emmetropes

	Myopes		Emmetropes	
Age	**OLSM**	**SCORM†**	**OLSM**	**SCORM**
8	0.28	0.39	0.15	0.14
9	0.25	0.31	0.13	0.11
10	0.30	0.25	0.09	0.09
11	0.22	0.20	0.07	0.08
12	0.20	0.17	0.06	0.06
13	0.19	0.14	0.06	0.06
14	0.18	0.12	0.05	0.05

All values are in mm. OLSM, Orinda Longitudinal Study of Myopia; SCORM, Singapore Cohort Study of the Risk Factors for Myopia.
†For the SCORM cohorts, equations for vitreous chamber depth elongation were used

Table 2. Predicted cumulative elongation at years 1, 2 and 3 for myopes and emmetropes using both the OLSM[7] and SCORM[37] models for a virtual cohort with the same age distribution as the MiSight clinical trial subjects

	"Virtual Cohort" myopes		MiSight trial myopes		"Virtual Cohort" emmetropes	
Duration	OLSM	SCORM	Control	Treated	OLSM	SCORM
1-year	0.25	0.26	0.24	0.09	0.10	0.09
2-year	0.48	0.46	0.45	0.21	0.18	0.17
3-year	0.70	0.63	0.62	0.30	0.24	0.24

Also shown are the values for cumulative axial elongation from the MiSight clinical trial.[34] All values are in mm. OLSM, Orinda Longitudinal Study of Myopia; SCORM: Singapore Cohort Study of the Risk Factors for Myopia.

(0.62 mm) to those predicted for the virtual cohorts of myopic children based on both the OLSM (0.70 mm) and SCORM (0.63 mm) models (*Table* 2). In contrast, the mean 3-year elongation in MiSight treated myopes is significantly lower (0.30) mm, and not substantially different from the predicted axial elongation rates for the virtual cohorts of emmetropes (0.24 mm, for both the OLSM and SCORM models).

Discussion

The mean axial elongation in children wearing Proclear single vision soft contact lenses in the MiSight clinical trial was 0.62 mm over 3 years,[34] which is very similar to that predicted for age-matched virtual cohorts of myopes using the growth models from OLSM and SCORM (0.70 and 0.63 mm, respectively). Other studies in the USA have reported similar mean 3-year elongation in cohorts with a comparable age distribution.[40,41] In contrast, the mean axial elongation in children wearing the dual-focus MiSight soft contact lenses was 0.30 mm over 3 years,[34] which is less than half that for the untreated control subjects and similar in magnitude to that predicted for age-matched virtual cohorts of emmetropes using the growth models from OLSM and SCORM (both 0.24 mm).[7,37]

It is noteworthy that emmetropic eyes in OLSM and SCORM continued elongating throughout childhood, albeit at a slower rate than myopic eyes.[7,37] Axial elongation continues into the late teens in both myopes[42] and emmetropes,[43] although only around 0.06 and 0.03 mm/year, respectively. In emmetropes, the ongoing axial elongation is compensated by crystalline lens flattening and thinning, such that refractive error does not change to a meaningful

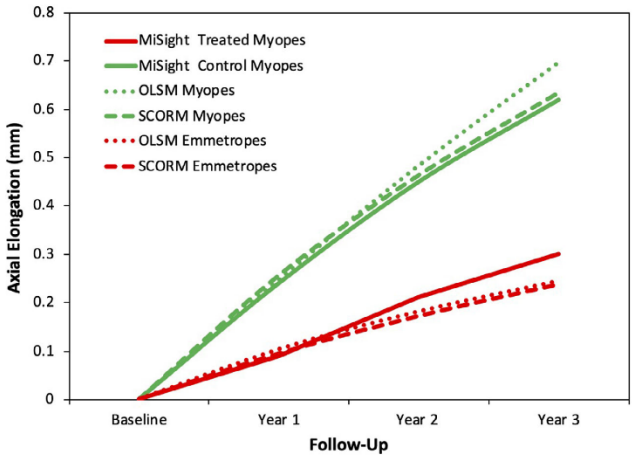


Figure 1. Cumulative axial elongation (mm) for treated and control myopes in the MiSight clinical trial are compared to the virtual myopic and emmetropic cohorts developed using both the OLSM[7] and SCORM[37] models (see Methods). OLSM: Orinda Longitudinal Study of Myopia; SCORM: Singapore Cohort Study of the Risk Factors for Myopia.

degree,[7,15,16] although the rate of crystalline lens change may not differ significantly between emmetropes and myopes[7] and some,[44] though not all,[45] studies have reported adult myopes to have thinner crystalline lenses than adult emmetropes. However, it is likely that crystalline lens thinning in myopes is simply insufficient to compensate for their more rapid axial elongation. Presumably ongoing eye growth in emmetropes reflects increases in body stature before, during and after puberty. Cross-sectional[46,47] and longitudinal studies[48] demonstrate an association between axial length and height, with taller emmetropic children having longer eyes. A recent longitudinal study demonstrated a high correlation between 2-year changes in height and axial length in emmetropes over two consecutive periods ($r = 0.71$ and 0.63), while myopes show no consistent association.[48] This leads to two hypotheses. First, *myopic* axial elongation is superimposed on this underlying *physiological* axial elongation. Second, optically based myopia control treatments may minimise the *myopic* axial elongation but may not be able to prevent the underlying *physiological* elongation. Based on the OLSM and SCORM growth curves, on average, emmetropic eyes elongate at 30% to 40% the rate of myopic eyes (*Table* 2, *Figure* 1).[7,37] The aforementioned hypotheses would thus predict that myopic control methods that slow progression by more than 60% to 70% in a population may be challenging to attain. In other words, the slowing of axial elongation in the MiSight clinical trial approaches the population limits placed upon therapy by physiological eye growth. It is noteworthy that no 2- or 3-year clinical trials of optical myopia control modalities exceed this value.[27]

Since this work was first presented,[49] the notion of underlying physiological growth has been embraced by others. Some presenters have also begun to adjust and re-quantify the efficacy of myopia control studies to claim higher percentage treatment effects based on this possible physiological eye growth.[50] There are, however, two reasons not to adopt this generalised approach of applying an arbitrary correction factor based on current understanding of eye growth. First, there is currently no evidence for two mechanisms (pathological and physiological) driving axial elongation. It is the total eye growth that is crucial to ocular health,[25] so distinctions between mechanisms of action may have no clinical ramifications. Second, any reports of percentage treatment efficacy are confounded by age, underlying progression rate and likely ethnicity.[26] Adjusting these rates for, as yet, unproven physiological growth would further obfuscate comparisons among myopia control therapies.

Although these data suggest that the MiSight dual-focus contact lens is able to slow eye growth to non-myopic levels, studies using daily dosing with higher concentrations of atropine (1%) have stopped eye growth. For example, the Atropine for the Treatment of Childhood Myopia (ATOM) Study reported a reduction in axial length (-0.14 ± 0.28 mm) in the first year for 166 eyes treated unilaterally with 1% atropine, followed by a + 0.12 mm elongation in the second year.[51] More recently, Yi *et al.*[52] reported virtually no change (-0.03 ± 0.07 mm) in 66 children treated bilaterally with 1% atropine for 1 year. These data suggest that, in the short-term, high concentrations of atropine may arrest axial elongation, although the mean elongation in the second year of the ATOM study is identical to that of treated eyes in the MiSight clinical trial data used for this study (*Table* 2). Unfortunately, atropine-treated eyes show a dramatic acceleration of myopia progression and axial elongation following cessation of treatment. The atropine-treated eyes in the ATOM study elongated by over 0.30 mm in the year following discontinuation of treatment, compared with around 0.15 mm in the untreated eyes.[53] Furthermore, concentrations as high as 0.5% have far less influence on axial elongation. For example, in a 2-year clinical trial, axial length increased by 0.27, 0.28 and 0.41 mm in subjects treated with 0.5%, 0.1% and 0.01%, respectively.[30]

The literature on optical interventions in animals has the potential to contribute to our understanding. Unfortunately, these experiments are typically conducted on neonatal animals, undergoing a rapid period of eye growth. For example, Hung *et al.*[54] demonstrated that +3 or +6 D lenses imposed in front of one eye of infant rhesus monkeys ranging from 72 to 113 days induced hyperopic anisometropia and a relative slowing of axial elongation in the treated eye. Nonetheless, while the treated eyes showed up to 0.4 mm less relative elongation, they still elongated by 1 to 2 mm. In other words, imposition of plus lenses did not completely arrest growth of infant eyes.

The comparison of axial elongation among untreated progressing myopes, treated progressing myopes and emmetropes has some limitations. The predicted axial elongation for age-matched virtual cohorts based on the growth curves published by OLSM and SCORM agree well with the reported mean axial elongation for the untreated myopes in the MiSight clinical trial. The ethnic composition of the children in the MiSight clinical trial includes a minority of Asian eyes, and is similar to the ethnic distribution within the OLSM cohort, although the studies were conducted over 20 years apart. For further comparison, the 3-year mean axial elongation for children wearing single vision spectacles in the Correction of Myopia Evaluation Trial (COMET) was 0.75 mm, but their mean age was younger by a year (9.3 ± 1.3 years).[31] Likewise, a clinical trial of myopic US children with a mean age of 10.4 ± 1.1 years at baseline reported mean 3-year axial elongation of 0.63 and 0.59 mm in those randomised to soft contact lenses ($n = 247$) and spectacles ($n = 237$),

respectively.[40] More recently, another study of US children ($n = 97$) with an average age of 10.3 ± 1.1 years randomised to single vision contact lenses in a myopia control clinical trial found a 3-year progression of 0.62 mm.[41] In summary, the mean axial elongation of the untreated myopes in the MiSight clinical trial is consistent with other similar aged cohorts.

Inspection of *Table* 1 demonstrates that the predicated elongation based on the SCORM model is higher than that for OLSM for 8 and 9 year olds, but the opposite is true for older children. As described earlier, the use of vitreous chamber depth was necessary and this may have underestimated axial elongation, given that increases in vitreous chamber depth account for around 90% of axial elongation.[6,55] Furthermore, the SCORM models are based on children no older than 12 years, and this may limit the accuracy of the growth curves at older ages.

While the SCORM model only represents data from children who are myopic at all timepoints,[37] the OLSM model includes both consistent and incident myopes.[7] As discussed in the introduction, axial elongation accelerates over a few years prior to myopia onset and is fastest in the 2 to 3 years immediately before onset. Thus, axial elongation in the SCORM model includes myopes in various phases of their refractive history. This can be partially quantified by comparing axial elongation rates from the SCORM model for both progressing and incident myopes (*Table* 3). At younger ages, the progressing myopes elongate faster, but by 10 or 11 years of age there is little difference.

As described in the Methods, there are differences between the OLSM and SCORM cohorts and the criteria adopted by the respective authors when developing their growth models. These may have contributed to discrepancies between the virtual cohorts derived from the models. OLSM followed children between 6 and 14 years, while SCORM studied children between 6 and 12 years. In OLSM, myopia was defined as at least –0.75 D in both meridians, whereas in SCORM the definition was at least –0.50 D spherical equivalent. Likewise, emmetropia was defined differently: –0.25 to +1.00 D in both meridians and –0.50 to +1.00 D spherical equivalent, respectively. OLSM used 1% tropicamide for cycloplegia, but SCORM used 1% cyclopentolate, although any differences attributed to these choices should be minimal.[56] Finally, among the children contributing to the OLSM models, 33.5% were myopic, compared with 68.6% of those for the SCORM models. It should also be noted that the MiSight clinical trial excluded children with astigmatism greater than 0.75 D, whereas both the OLSM and SCORM models appear to have included myopes regardless of astigmatism. Given the association of myopia with astigmatism,[57,58] this may have influenced our findings, but it is unclear in which direction.

Table 3. Annual vitreous chamber elongation as a function of age (in years) predicted by the SCORM[37] models for progressing and incident myopes

Age	Progressing myopes	Incident myopes
8	0.39	0.32
9	0.31	0.27
10	0.25	0.23
11	0.20	0.19
12	0.17	0.16
13	0.14	0.14
14	0.12	0.12

All values are in mm.
SCORM, Singapore Cohort Study of the Risk Factors for Myopia.

A curious feature of the axial elongation rate of the predominantly Singaporean Chinese myopes in SCORM is that it is similar in magnitude to the rate in OLSM. It would be expected that the axial elongation for myopes in the SCORM model would be higher given that the rates of myopic progression[59] and axial elongation[13] are 50% higher among myopes in Asia compared to children of European descent. Both OLSM and SCORM used ultrasound to measure axial length, while the MiSight clinical trial used the IOLMaster. While the latter technique has superior repeatability, any systematic differences between the methods is small and invariant with axial length. Such small differences are very unlikely to affect the applicability of models of axial elongation based on one technique to measures made with the other.[60,61]

When comparing axial elongation among refractive groups, it must be acknowledged that emmetropic eyes are, on average, shorter than myopic eyes. Thus, the comparisons between myopes undergoing myopia control treatment in the MiSight clinical trial with emmetropes might be improved by matching the groups for baseline axial length. The mean baseline axial length of the MiSight treated myopes was 24.42 mm, whereas an age-matched virtual cohort of emmetropes would be 23.66 and 23.32 mm, based on the OLSM and SCORM models, respectively. As shown in *Table* 3, the SCORM authors publish separate growth curves based on both 616 progressing myopes (used herein) and 601 incident myopes, i.e., emmetropes who become myopes. As would be expected the modelled axial length is around 0.08 mm shorter in the incident myopes compared to the progressing myopes, but the predicted rate of axial elongation (*Table* 3) differs by no more than 0.02 mm per year beyond 10 years of age. Furthermore, neither the OLSM nor SCORM models factor in baseline eye size. However, there was no correlation between baseline axial length and 3-year elongation in the MiSight clinical trial, although this and other trials show that axial elongation is slower in those who were older at

baseline.[34,40] Indeed, data from this MiSight study shows that when the control group illustrated in this analysis were switched to the MiSight lens at an average age of 13.1 years, the subsequent 2-year axial elongation was equivalent to that of the original MiSight group continuing in treatment, despite the fact that the original control group commenced the 2-year assessment period with greater refractive error and longer eyes, as a result of the treatment effect in the first 3 years of the trial.

Finally, this analysis represents average change across a population of children. Individuals within a population display great variation; for example, the standard deviations for axial elongation for the 3-year MiSight clinical trial were 0.27 and 0.30 mm in the treated and control groups, respectively.[34] The same is true for refractive error with some treated children showing myopia progression similar to the mean progression in untreated children. Conversely, some treated children and very few untreated children show almost no progression. For example, in the MiSight clinical trial, 41% of treated eyes showed −0.25 D or less progression over 3 years compared with 4% of the eyes in the control group. Future research may explain why some subjects progress less than others, and the factors that affect the variation in treatment effect. This may lead to improved treatments, as the search for optimal myopia control modalities is still in its early stages.

In summary, the untreated myopes in the MiSight clinical trial show 3-year axial elongation similar to control myopes in other clinical trials[31,40] and similar to that predicted from models of eye growth based on large cohorts.[7,37] The myopes treated with the MiSight lens show similar 3-year axial elongation to that of emmetropes predicted by models of eye growth. It is proposed that axial elongation in patients undergoing myopia control be considered in the context of both normal myopic and emmetropic eye growth and expectations be set accordingly. Nonetheless, arbitrary correction factors to account for the impact of physiological eye growth should not be applied when reporting myopia control levels, until this area has been better understood.

Conflict of interest

Paul Chamberlain, Percy Lazon and Baskar Arumugam are employees of CooperVision. Mark Bullimore is a consultant for Alcon Research, Inc., Apellis, Inc., Arctic Vision, Inc., Ascpleix, Inc., CooperVision, Inc., Corneagen, Inc., Essilor International S.A.., Eyenovia, Inc., Genentech, Inc., Johnson & Johnson Vision, Inc., Presbia, Inc., and is the sole owner of Ridgevue Publishing, LLC, Ridgevue Technologies LLC, and Ridgevue Vision LLC. Preparation of this paper was supported by CooperVision, Inc.

Author contributions

Paul Chamberlain: Conceptualization (equal); Data curation (equal); Investigation (equal); Writing-review & editing (equal). **Percy Lazon:** Writing-review & editing (equal). **Baskar Arumugam:** Writing-review & editing (equal). **Mark Bullimore:** Formal analysis (equal); Methodology (equal); Writing-original draft (lead).

References

1. Grosvenor T & Goss DA. Role of the cornea in emmetropia and myopia. *Optom Vis Sci* 1998; 75: 132–145.
2. Grosvenor T & Scott R. Role of the axial length/corneal radius ratio in determining the refractive state of the eye. [See Comments] *Optom Vis Sci* 1994; 71: 573–579.
3. Rozema JJ, Atchison DA & Tassignon MJ. Comparing methods to estimate the human lens power. *Invest Ophthalmol Vis Sci* 2011; 52: 7937 7942.
4. Cruickshank FE & Logan NS. Optical 'Dampening' of the refractive error to axial length ratio: implications for outcome measures in myopia control studies. *Ophthalmic Physiol Opt* 2018; 38: 290–297.
5. Tideman JWL, Polling JR, Vingerling JR *et al.* Axial length growth and the risk of developing myopia in European children. *Acta Ophthalmol* 2018; 96: 301–309.
6. Mutti DO, Sinnott LT, Mitchell GL *et al.* Ocular component development during infancy and early childhood. *Optom Vis Sci* 2018; 95: 976–985.
7. Jones LA, Mitchell GL, Mutti DO *et al.* Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci* 2005; 46: 2317–2327.
8. Mutti DO, Hayes JR, Mitchell GL *et al.* Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci* 2007; 48: 2510–2519.
9. Mutti DO, Mitchell GL, Jones LA *et al.* Axial growth and changes in lenticular and corneal power during emmetropization in infants. *Invest Ophthalmol Vis Sci* 2005; 46: 3074–3080.
10. Xiang F, He M & Morgan IG. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. *Ophthalmology* 2012; 119: 1478–1484.
11. Rozema J, Dankert S, Iribarren R *et al.* Axial growth and lens power loss at myopia onset in Singaporean children. *Invest Ophthalmol Vis Sci* 2019; 60: 3091–3099.
12. Chua SY, Sabanayagam C, Cheung YB *et al.* Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt* 2016; 36: 388–394.
13. Brennan N, Cheng X, Toubouti Y & Bullimore M. Influence of age and race on axial elongation in myopic children. *Optom Vis Sci* 2018; 95: E-abstract 180072.

14. COMET Group. Myopia stabilization and associated factors among participants in the correction of myopia evaluation trial (COMET). *Invest Ophthalmol Vis Sci* 2013; 54: 7871–7884.
15. Mutti DO, Zadnik K, Fusaro RE *et al.* Optical and structural development of the crystalline lens in childhood. *Invest Ophthalmol Vis Sci* 1998; 39: 120 133.
16. Mutti DO, Mitchell GL, Sinnott LT *et al.* Corneal and crystalline lens dimensions before and after myopia onset. *Optom Vis Sci* 2012; 89: 251–262.
17. Zadnik K, Mutti DO, Fusaro RE & Adams AJ. Longitudinal evidence of crystalline lens thinning in children. *Invest Ophthalmol Vis Sci* 1995; 36: 1581–1587.
18. Wolffsohn JS, Kollbaum PS, Berntsen DA *et al.* IMI - Clinical myopia control trials and instrumentation report. *Invest Ophthalmol Vis Sci* 2019; 60: M132–M160.
19. Bullimore MA & Brennan NA. Myopia control: why each diopter matters. *Optom Vis Sci* 2019; 96: 463–465.
20. Haarman AEG, Enthoven CA, Tideman JWL *et al.* The complications of myopia: a review and meta-analysis. *Invest Ophthalmol Vis Sci* 2020; 61: ARVO E-Abstract 49.
21. Vongphanit J, Mitchell P & Wang JJ. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology* 2002; 109: 704–711.
22. Ramakrishnan R, Nirmalan PK, Krishnadas R *et al.* Glaucoma in a rural population of Southern India: the Aravind comprehensive eye survey. *Ophthalmology* 2003; 110: 1484–1490.
23. Wong TY, Foster PJ, Johnson GJ & Seah SK. Refractive errors, axial ocular dimensions, and age-related cataracts: the Tanjong Pagar survey. *Invest Ophthalmol Vis Sci* 2003; 44: 1479–1485.
24. Risk factors for idiopathic rhegmatogenous retinal detachment. The Eye Disease Case-Control Study Group. *Am J Epidemiol* 1993; 137: 749–757.
25. Tideman JW, Snabel MC, Tedja MS *et al.* Association of axial length with risk of uncorrectable visual impairment for europeans with myopia. *JAMA Ophthalmol* 2016; 134: 1355–1363.
26. Brennan NA, Toubouti YM, Cheng X & Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res* 2020; 27: 100923. https://doi.org/10.1016/j.preteyeres.2020.100923. Accessed 19 Mar 2021. Epub ahead of print. PMID: 33253901.
27. Wildsoet CF, Chia A, Cho P *et al.* IMI - Interventions myopia Institute: interventions for controlling myopia onset and progression report. *Invest Ophthalmol Vis Sci* 2019; 60: M106–M131.
28. Bullimore MA & Richdale K. Myopia control 2020: where are we and where are we heading? *Ophthalmic Physiol Opt* 2020; 40: 254 270.
29. Bullimore MA & Berntsen DA. Low-dose atropine for myopia control: considering all the data. *JAMA Ophthalmol* 2018; 136: 303.
30. Chia A, Chua WH, Cheung YB *et al.* Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). *Ophthalmology* 2012; 119: 347–354.
31. Gwiazda J, Hyman L, Hussein M *et al.* A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci* 2003; 44: 1492–1500.
32. Walline JJ, Jones LA, Mutti DO & Zadnik K. A randomized trial of the effects of rigid contact lenses on myopia progression. *Arch Ophthalmol* 2004; 122: 1760–1766.
33. Cheng D, Woo GC, Drobe B & Schmid KL. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. *JAMA Ophthalmol* 2014; 132: 258–264.
34. Chamberlain P, Peixoto-de-Matos SC, Logan NS *et al.* A 3-year randomized clinical trial of misight lenses for myopia control. *Optom Vis Sci* 2019; 96: 556–567.
35. Chamberlain P, Arumugam B, Jones D *et al.* Myopia progression in children wearing dual-focus contact lenses: 6-year findings. *Optom Vis Sci* 2020; 97: E-abstract 200038.
36. Kleinstein RN, Sinnott LT, Jones-Jordan LA *et al.* New cases of myopia in children. *Arch Ophthalmol* 2012; 130: 1274–1279.
37. Wong HB, Machin D, Tan SB *et al.* Ocular component growth curves among singaporean children with different refractive error status. *Invest Ophthalmol Vis Sci* 2010; 51: 1341–1347.
38. Zadnik K, Mutti DO, Friedman NE & Adams AJ. Initial cross-sectional results from the Orinda longitudinal study of myopia. *Optom Vis Sci* 1993; 70: 750–758.
39. Saw SM, Tong L, Chua WH *et al.* Incidence and progression of myopia in Singaporean school children. *Invest Ophthalmol Vis Sci* 2005; 46: 51–57.
40. Walline JJ, Jones LA, Sinnott L *et al.* A randomized trial of the effect of soft contact lenses on myopia progression in children. *Invest Ophthalmol Vis Sci* 2008; 49: 4702 4706.
41. Walline JJ, Walker MK, Mutti DO *et al.* Effect of high add power, medium add power, or single-vision contact lenses on myopia progression in children: the blink randomized clinical trial. *JAMA* 2020; 324: 571–580.
42. Hou W, Norton TT, Hyman L *et al.* Axial elongation in myopic children and its association with myopia progression in the correction of myopia evaluation trial. *Eye Contact Lens* 2018; 44: 248–259.
43. Hagen LA, Gilson SJ, Akram MN & Baraas RC. Emmetropia is maintained despite continued eye growth from 16 to 18 years of age. *Invest Ophthalmol Vis Sci* 2019; 60: 4178–4186.
44. McBrien NA & Millodot M. A biometric investigation of late onset myopic eyes. *Acta Ophthalmol (Copenh)* 1987; 65: 461 468.
45. Bullimore MA, Gilmartin B & Royston JM. Steady-state accommodation and ocular biometry in late-onset myopia. *Doc Ophthalmol* 1992; 80: 143–155.
46. Saw SM, Chua WH, Hong CY *et al.* Height and its relationship to refraction and biometry parameters in Singapore

Chinese children. *Invest Ophthalmol Vis Sci* 2002; 43: 1408–1413.
47. Wang D, Ding X, Liu B *et al.* Longitudinal changes of axial length and height are associated and concomitant in children. *Invest Ophthalmol Vis Sci* 2011; 52: 7949–7953.
48. Kearney S, Strang NC, Cagnolati B & Gray LS. Change in body height, axial length and refractive status over a four-year period in Caucasian children and young adults. *J Optom* 2020; 13: 128–136.
49. Logan N. Conference report: the 16th International myopia conference. *Ophthalmic Physiol Opt* 2018; 38: 215–216.
50. Rappon J, Neitz J, Neitz M & Chalberg T. A new method for determining an age-independent axial length percentage reduction for myopia therapies. *Optom Vis Sci* 2020;97: E-abstract 205349.
51. Chua WH, Balakrishnan V, Chan YH *et al.* Atropine for the treatment of childhood myopia. *Ophthalmology* 2006; 113: 2285–2291.
52. Yi S, Huang Y, Yu SZ *et al.* Therapeutic effect of atropine 1% in children with low myopia. *J AAPOS* 2015; 19: 426–429.
53. Tong L, Huang XL, Koh AL *et al.* Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology* 2009; 116: 572–579.
54. Hung LF, Crawford ML & Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med* 1995; 1: 761–765.
55. Hyman L, Gwiazda J, Hussein M *et al.* Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol* 2005; 123: 977–987.
56. Mutti DO, Zadnik K, Egashira S *et al.* The effect of cycloplegia on measurement of the ocular components. *Invest Ophthalmol Vis Sci* 1994; 35: 515–527.
57. Tong L, Saw SM, Carkeet A *et al.* Prevalence rates and epidemiological risk factors for astigmatism in Singapore school children. *Optom Vis Sci* 2002; 79: 606–613.
58. O'Donoghue L, Rudnicka AR, McClelland JF *et al.* Refractive and corneal astigmatism in white school children in Northern Ireland. *Invest Ophthalmol Vis Sci* 2011; 52: 4048–4053.
59. Donovan L, Sankaridurg P, Ho A *et al.* Myopia progression in Chinese children is slower in summer than in winter. *Optom Vis Sci* 2012; 89: 1196–1202.
60. Carkeet A, Saw SM, Gazzard G *et al.* Repeatability of Iol-master biometry in children. *Optom Vis Sci* 2004; 81: 829–834.
61. Sheng H, Bottjer CA & Bullimore MA. Ocular component measurement using the Zeiss Iolmaster. *Optom Vis Sci* 2004; 81: 27–34.

6.5. Publication: Six-year cumulative treatment effect and treatment efficacy of a dual focus myopia control contact lens

Received: 27 June 2023 | Accepted: 10 October 2023 | Published online: 27 October 2023

DOI: 10.1111/opo.13240

OPO THE COLLEGE OF OPTOMETRISTS

ORIGINAL ARTICLE

Six-year cumulative treatment effect and treatment efficacy of a dual focus myopia control contact lens

Paul Chamberlain | **David Scott Hammond** | **Baskar Arumugam** | **Arthur Bradley**

Cooper Vision Inc., San Ramon, California, USA

Correspondence
Paul Chamberlain, Cooper Vision Inc., San Ramon, CA, USA.
Email: pchamberlain@coopervision.com

Funding information
CooperVision

Abstract

Purpose: Accumulated axial growth observed during a 6-year clinical trial of a dual focus myopia control contact lens was used to explore different approaches to assess treatment efficacy.

Methods: Axial length measurements from 170 eyes in a 6-year clinical trial of a dual focus myopia control lens (MiSight 1 day, CooperVision) were analysed. Treatment groups comprised one having undergone 6 years of treatment and the other (the initial control group) having 3 years of treatment after 3 years of wearing a single vision control lens. Efficacy was assessed by comparing accumulated ocular growth during treatment to that expected of untreated myopic and emmetropic eyes. The impact of treatment on delaying axial growth was quantified by comparing the increased time required to reach criterion growths for treated eyes and survivor analysis approaches.

Results: When compared to the predicted accumulated growth of untreated eyes, 6 years of treatment reduced growth by 0.52 mm, while 3 years of treatment initiated 3 years later reduced growth by 0.19 mm. Accumulated differences between the growth of treated and untreated myopic eyes ranged between 67% and 52% of the untreated myopic growth, and between 112% and 86% of the predicted difference in growth between untreated myopic and age-matched emmetropic eyes. Treated eyes took almost 4 years longer to reach their final accumulated growth than untreated eyes. Treatment increased the time to reach criterion growths by 2.3–2.7 times.

Conclusion: Estimated growth of age-matched emmetropic and untreated myopic eyes provided evidence of an accumulated slowing in axial elongation of 0.52 mm over 6 years, and the treated growth remained close to that expected of emmetropic eyes. Six years of dual focus myopia control delayed the time to reach the final growth level by almost 4 years.

KEYWORDS
axial length, contact lenses, emmetropic eye growth, myopia, myopia control, myopia progression

INTRODUCTION

Axial growth of the vitreous chamber, unaccompanied by compensatory reductions in optical power in the cornea or lens,[1,2] is generally responsible for myopia development. Recent increases in myopia prevalence are present globally and most striking in young adults in east Asia where the vast majority of eyes are myopic.[3–5] Longer eyes, responsible for higher levels of myopia, are associated with an increased risk of maculopathy and other sight-threatening pathologies later in life,[6–8] and with reduced best-corrected visual acuity earlier in life.[9] Numerous optical interventions have

been employed to slow or stop this progressive condition, some proving effective in slowing axial growth and myopia progression over 2 or 3 years of treatment.[10–12] Efficacy of these myopia control interventions has been established by implementing rigorous randomised controlled trial (RCT) protocols. However, since treatments with proven efficacy have become available, ethical and practical concerns,[13] specifically recruitment and retention of control groups for long periods, have necessitated alternate study designs to evaluate efficacy that do not retain a control group for the full study duration. For example, cross-over[14] comparisons with pre-treatment[15] and delay in reaching a criterion level[16] have all been employed to assess treatment efficacy. Also, due to the wealth of published data on axial growth in myopic and emmetropic eyes,[17–19] the growth of treated eyes can be compared with the growth of untreated myopic and age-matched emmetropic eyes from other studies.[20–23]

Myopia is a progressive condition which can start in early childhood with a mean onset of approximately 8 years of age[24] and a mean age of stabilisation of approximately 15 years.[25,26] Earlier onset is associated with faster progression, as well as the possibility of a longer duration of progression resulting in higher levels of myopia.[24] Therefore, myopia control treatments may need to be effective over multiple years and be suitable for both children and adolescents. To explore the multi-year long-term effects of treatment with a dual focus myopia control contact lens that has been proven effective in controlling myopia and axial growth during a 3-year RCT,[10] both the initially treated and untreated control groups were fitted with the dual focus lenses for a second 3-year study period.[15] Although this transitioning of the initial control group to treatment resolved ethical concerns of leaving them untreated after the dual focus lenses had proven effective, it created challenges for assessing efficacy because axial growth of the treated eyes during Years 4 through 6 could not be compared with concurrent control eyes. In this report, the accumulated 6-year data from the MiSight 1 day clinical trial[15] were used to examine four different approaches for assessing efficacy by comparing axial growth of treated eyes to that observed in: (1) a concurrent matched control group (Years 1–3)[10]; (2) untreated myopic eye growth applied to the known rates of the observed control cohort as reported in the literature (Years 4–6)[21]; (3) reported age-matched growth of non-myopic (emmetropic) eyes[20] and (4) the ability of treatment to delay a criterion level of progression in months or years.[13,16]

Key points

- In the absence of a control group, prior myopia progression, emmetropic eye growth and delay in time to progress analysis methods can be used to estimate myopia control efficacy.
- During each of six treatment years, a dual focus soft contact lens slowed eye growth to less than half of that observed in untreated individuals, paralleling modelled emmetropic growth rates.
- When myopic individuals begin wearing dual focus soft contact lenses between 8 and 12 years of age, the probability of ≥0.3 mm eye growth occurring within 1–3 years decreases by 95%.

METHODS

Study design

Details of the 6-year clinical trial were described by Chamberlain.[10,15] After the completion of the 3-year Part 1 multicentre, double-masked, randomised, controlled clinical trial (ClinicalTrials.gov Identifier: NCT01729208), the investigation became an open-label study in which all eyes were treated without masking or randomisation. All subjects who successfully completed Part 1 (36 months) were invited to enrol in Part 2, during which all eyes were fitted with the dual focus myopia control lenses (MiSight 1 day, omafilcon A, misight.com). Initial visits for Part 2 took place immediately following the 36-month exit visit and re-consent occurred between December 2015 and February 2017. Subjects remained masked to their Part 1 cohort assignment. Both parts of the trial were conducted at the same four investigational sites (University of Minho, Portugal; Aston University, UK; National University Hospital, Singapore and the University of Waterloo, Canada) and registered under the same identifier. The study was conducted in conformance with the ethical principles of the Declaration of Helsinki, with the International Council for Harmonisation guidelines for Good Clinical Practice and all applicable local regulations. It was reviewed by an independent ethical review board and conformed with the principles and applicable guidelines for the protection of human subjects in biomedical research. Axial length was measured using an optical biometer (IOL Master 500; Carl Zeiss, zeiss.com) with cycloplegia being induced with two drops of 1% tropicamide instilled 5 min apart. The 6-year accumulated growth analysis was performed only on the 170 eyes from 85 subjects who completed the 6-year study.

Efficacy analysis

The effectiveness in slowing axial growth was assessed by comparing the growth of treated eyes to three different benchmarks. (1) A concurrent *untreated* myopic control was available for Years 1–3. (2) Prior published growth data for age-matched *untreated* myopic eyes from a meta-analysis of 78 axial length studies that identified a simple exponential decay in growth rate (growth in Year $n = 0.85 \times$ growth in Year $n-1$) of myopic eyes as they age.[19] This exponential

growth rule was used to estimate annual and thus cumulative axial growth for the control group following 1 and 3 years of measured growth. (3) The axial growth of age-matched emmetropic eyes[17] was used to compare treated axial growth to that expected of non-myopic eyes. Efficacy was assessed based on growth relative to that expected in an age-matched emmetropic population. The functions fitted to the axial growth of emmetropic eyes (Ages 6–14) from the Orinda Longitudinal Study of Myopia (OLSM)[17] were used to compile weighted average expected axial length growth for the age distribution of our sample.[20] (4) Instead of assessing treatment efficacy in millimetres, a fourth approach assessed the increased time in months or years taken for the treated eyes to reach a criterion growth. Time at which eyes under continued treatment reach the criterion growth after the control group has been terminated can, therefore, contribute to the assessment of efficacy. In addition to performing this analysis on the cohort mean data, the time to reach a criterion growth for each individual eye was quantified and myopia progression expressed as a binary outcome (i.e., growth has or has not reached criterion).[27] This survival analysis was performed using the R statistical software (r-project.org, version 4.1.1) assessing the time that individual eyes took to reach a criterion ≥0.3 mm axial growth, which represents a close axial length approximation to a 0.75 D criterion suggested by others.[28] The Kaplan–Meier method was used to estimate the survival curves for each contact lens type (single vision vs. dual focus). Log-rank tests were performed to compare the survival curves between the lens treatment groups with Cox proportional hazard models. Survival plots were generated using the 'survminer' package within R to visualise survival curves for each lens types.

RESULTS

Axial length growth from the initial baseline visit was plotted for the group who wore the treatment lens for all 6 years (T6, $n = 80$ eyes) and for those who only received treatment during the final 3 years (T3, $n = 90$ eyes). These average data were compared to previously published average values for age-matched myopic[19] and emmetropic axial length growth[17] (Figure 1).

Axial length growth from baseline for the T6 treated eyes was compared directly with the growth of the control group for Years 1–3,[10] and then with a virtual control group for the subsequent Years 4–6.[19] To assess the appropriateness of the myopic eye growth model to the study data, the cumulative growth of untreated myopic eyes predicted by the model (observed Year 1 growth plus the predicted 15% slower growth during each subsequent year[19]) was compared to the observed growth of the untreated control eyes during Years 2 and 3. Differences between model and observed cumulative growths were negligible (0.01 and 0.001 mm at Years 2 and 3, respectively) indicating the close alignment of both model and observed untreated

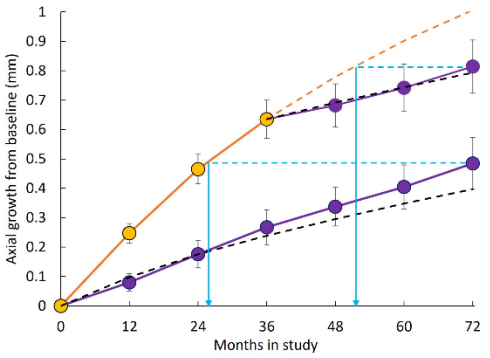


FIGURE 1 Average axial length change from baseline for the cohorts who completed the 6-year study and either received treatment for all 6 years/72 months (T6) or were untreated for Years 1–3 and received treatment for Years 4–6/36–72 months (T3). Average growth expected for age-matched emmetropic (black dashed lines, Orinda Longitudinal Study of Myopia (OLSM)[17]) and myopic (orange dashed lines, meta-analysis[19]) eyes were plotted along with the observed axial length growth of study eyes during treatment (purple solid lines) or when untreated (control eyes during Part 1, orange solid lines). Horizontal blue dashed lines indicate the final (72 month) growth of treated eyes, while blue arrows indicate the study duration required for untreated eyes to reach these levels. Error bars are ±2 SEM.

growth in the current data set. Using the observed growth during Year 3 of the control group and the 15% slowing during each subsequent year, the estimated growth of the control eyes if left untreated was used as a 'virtual control' during Years 4–6 (Figure 1, orange dashed curve). Accumulated differences in axial length growth for T6 eyes increased during each treatment year, reaching 0.37 mm at the completion of Part 1 and 0.52 mm at the end of Year 6 (Table 1). Using the same virtual control, the axial growth of the T3 group also slowed during each treatment year with an accumulated slowing of 0.19 mm over treated Years 4–6 (Table 1). When the difference in growth between the treated eyes and the controls was computed as a percentage of the untreated growth, the accumulating treatment effects remained approximately stable over 6 years, showing a decline from 68% to 67% slowing during the first year of treatment to 52% by the last year of treatment.

Figure 1 also plots the estimated average axial growth of an emmetropic population[17] having the same age distribution as the experimental group (black dashed lines) and reveals the slower growth of emmetropes relative to untreated myopic eyes. Expected emmetropic growth during Years 1–6 has been plotted relative to the axial length at baseline for comparison with the T6 data, and relative to the axial length observed at 36 months for the T3 group. In both cases, the similarity of the observed treated axial length growth and the expected growth for age-matched emmetropes reveals that eyes treated with the dual focus myopia control contact lens were growing at rates approximating those expected in age-matched emmetropic

TABLE 1 Cumulative treatment efficacy for each successive treatment year of the T6 and T3 cohorts. T6 and T3 indicate the two treatment groups that either underwent 6 years of treatment or 3 years of treatment after 3 years of wearing a single vision control lens, respectively.

	Study years					
	1	2	3	4	5	6
T6						
T – U (mm)	−0.17	−0.29	−0.37	−0.44	−0.50	−0.52
(T – U)/U (%)	68	62	58	57	55	52
T – E (mm)	−0.02	0.00	0.03	0.04	0.06	0.09
(T – U)/(E – U) (%)	112	100	93	91	90	86
T3						
T – U (mm)				−0.10	−0.16	−0.19
(T – U)/U (%)				67	60	52
T – E (mm)				−0.01	0.00	0.02
(T – U)/(E – U) (%)				110	101	90

Note: Efficacy was defined by the difference in axial growth in treated (T) and untreated (U) eyes in mm (T – U) and as a percentage of the untreated growth ((T – U)/U). Efficacy was also defined by the difference in treated (T) and emmetropic (E) growth in millimetres (T – E) and as a percentage of the untreated myopic growth that exceeded expected emmetropic growth (T – U)/(E – U). Negative values indicate that the treated eyes grew slower than the comparators.

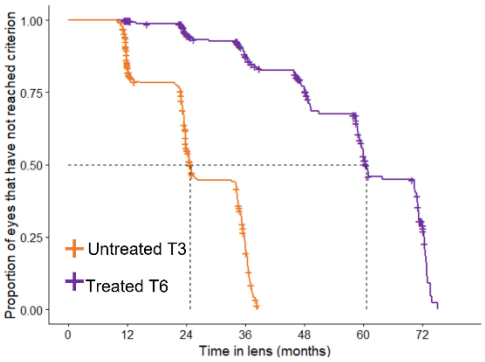


FIGURE 2 The probability of an eye not reaching a criterion cumulative growth of 0.3 mm from baseline plotted as a function of time after baseline for the untreated control eyes (T3 years 1–3, orange) and the dual focus myopia control treated eyes (T6 years 1–6, purple). The horizontal dashed line at 0.50 on the *y*-axis represents the point where 50% of the eyes in the cohort have reached or surpassed the eye growth criterion (≥0.3 mm). The corresponding vertical dashed line for each lens type denotes the time-to-event, that is how long it took 50% of eyes to reach the growth criterion. T6 and T3 indicate the two treatment groups that either underwent 6 years of treatment or 3 years of treatment after 3 years of wearing a single vision control lens, respectively.

eyes. The resulting observed slowing (difference between untreated and treated eyes in millimetres) as a percentage of the differences expected between myopic and emmetropic eyes is another estimate of efficacy (slowed growth as a percentage of the extra myopic growth in the untreated eyes, Table 1). If returning the accelerated axial growth of a myopic population to emmetropic levels is a target for 100% efficacy, then the similarity of growth in dual focus treated and emmetropic eyes suggests a high efficacy was achieved, with average slowing of growth ranging between 112% and 86% of this emmetropic target (Table 1).

An alternative approach for assessing efficacy quantifies the treatment effect as a slowing in time of the progression, for example, the increased time to reach a criterion progression transforming the results from technical units of mm to familiar units of time. Two examples of this approach are shown in Figure 1 (blue dashed lines), in which the time taken by untreated eyes to reach the final growth levels of treated eyes was assessed. The 0.48 mm of growth observed after 72 months of treatment was reached by the control eyes after only 25.4 months, revealing a treatment induced delay in growth of 3 years and 11 months, or alternatively an increase in the time to reach this growth level of 2.8 times. A similar analysis for the eyes treated only during the second 3-year period showed that the treated growth after 3 years of treatment was reached after 15.4 months in untreated eyes; a 2.3 times delay in growth.

The treatment effect, defined as time to reach a criterion growth, can also be quantified by setting a criterion and observing how long treated and untreated eyes can 'survive' before reaching the criterion growth. Such a 'survival analysis'[13,16,27] was used to plot the likelihood that a given eye in the current 6-year study had *not reached* a criterion axial length growth for both the untreated eyes measured during Years 1–3, and the treated T6 eyes measured over the 6-year trial. The resulting step-like plots (Figure 2) do not reflect sudden bursts of growth but rather the episodic (yearly) measurement cycles at which growth could be assessed, and indicate the likelihood that the criterion growth was achieved sometime during the year prior to the time when measurements were taken. Using a criterion of 0.3-mm axial growth, the median time to this event was 24.8 months (95% CI: 24.5,

25.9) for untreated control eyes and 60.6 months (95% CI: 59.8, 70.4) for dual focus treated eyes, increasing the survival time by 35 months or 2.9 years (slowing by a factor of 2.4). The Cox proportional hazard ratio gives an indication of the cumulative risk of axial growth occurring over a specified time-period compared to placebo.[27] The hazard ratio is calculated by dividing the risk of treated eyes reaching the criterion in the 3-year interval by the risk of untreated eyes reaching the same criterion. When these risks were compared over 3 years (years 1–3) for the 0.3-mm criterion, the Cox hazard ratio was 0.05 (95% CI: 0.04, 0.07), indicating a significantly ($p < 0.0001$) reduced risk of 0.3-mm axial length progression for eyes fitted with the dual focus myopia control lens. Alternatively stated, dual focus lens wear reduced the likelihood of 0.3 mm of axial progression by 95% over a 3-year time-period when compared with a single-vision correction.

DISCUSSION

Ethical and practical concerns motivated a change from a two-arm RCT of a dual focus myopia control contact lens to an open label study design at 36 months in which all eyes were subsequently treated during Years 4–6.[15] This change at 36 months eliminated direct comparison between the observed axial growth of treated eyes during Years 4–6 and a concurrent control group of untreated eyes; a situation faced by others in the myopia control field who conduct clinical trials beyond initial proof of efficacy.[29] This analysis examined some alternative approaches for estimating efficacy in the absence of the concurrent control by employing prior reported average myopic[19] and emmetropic[17] axial growth as comparators (Figure 1), and also examining the delay in time to progress by criterion amounts (Figures 1 and 2). These approaches allowed the accumulated treatment effects of the dual focus contact lens to be assessed over the full 6 years of treatment (Table 1).

Employing a virtual control group provides a convenient strategy to avoid denying treatment to myopic children assigned to a control group but lacks the assured cohort matching achieved by randomisation and inclusion criteria.[30] Therefore, the estimates of efficacy based upon virtual control groups may be less accurate than those achieved with a concurrent matched control group. The close match between the virtual control growth data and our observed control data (Figure 1) during Years 2–3 provides confidence that the virtual myopic axial length growth control group was representative of our cohort. Such an approach of employing measured pre-treatment growth to customise generic growth models may have widespread applicability in continued assessment of efficacy when a control group is no longer available. This approach provided evidence of an accumulated slowing of axial elongation of 0.52 mm over the 6 years of treatment. The data show a widening gap between treated and untreated growth (Figure 1), establishing a year-on-year accumulation of treatment effect (Table 1) with the dual focus lens. The observed treatment effect in the first year accounted for 33% of the total treatment effect over 6 years. These results do not support the view that treatment largely works for only 1 year. Absolute treatment (slowed growth in millimetres) varies from year to year, generally declining as the children age.

Treated eyes slowed axial growth to slightly less than half of that observed in untreated eyes and within a few percentage points of emmetropic eyes. Comparison of treated axial length growth to emmetropic eye growth[20,22,23] generates another opportunity for assessing treatment efficacy. The standard approach of quantifying slowed growth as a percentage of untreated growth will achieve 100% efficacy if treated eyes were to stop growing completely. However, young eyes can continue to grow into the teenage years without generating myopia.[17,18] If emmetropic growth is considered a treatment target, then efficacy may be considered as 100% if the treated axial length growth slows to levels seen in an age-matched emmetropic population. By this criterion, the dual focus contact lens achieved efficacies ranging from 86% to 112%. However, when using prior published data for untreated myopic axial length growth for comparison, estimates of treatment efficacy using age-matched emmetropic axial length growth from prior publications may not be as accurate as those derived from an age- and demographically matched concurrent emmetropic control group. Also, the myopic eyes recruited into this 6-year study were already larger than age-matched emmetropic eyes due to their already existing myopia, and therefore it is crucial to emphasise that slowing axial length growth to emmetropic rates does not equate to returning eye size to emmetropic levels. Growth rates would have to be slowed to less than emmetropic rates, or in some cases reversed in order to achieve an emmetropic eye size.

Although treatment slowed axial growth to levels similar to those seen in age-matched emmetropic eyes, myopia progression did not stop, but rather continued at a slowed rate.[10,15] Emmetropic growth rates in already myopic eyes may not ensure emmetropia because of an absence of the compensatory optical changes responsible for maintaining emmetropia that are active in growing emmetropic eyes.[18,31] These data suggest that the human crystalline lens may be limited in its ability to reduce power in response to axial elongation, and this limit will be selectively manifest in faster growing myopic eyes resulting in greater 'uncompensated growth'.[31] Consistent with the hypothesis that axial growth in treated myopic eyes is uncompensated by reduced power of the lens, emmetropic levels of axial growth in treated eyes were associated with slowed but not zero myopia progression.[31] Future treatments may go beyond both benchmarks and return a large progressing myopic eye to a refractive and axial emmetropic status.

Using either cohort mean analysis or individual eye survival analysis, the efficacy of the dual focus myopia control lens can be quantified by the delay to progress to some

criterion level and the associated reduced risk of developing a criterion level of growth (Figures 1 and 2). Eye growth after 6 years of treatment was reached in approximately 2 years by the untreated eyes, emphasising the dramatic slowing of growth during treatment. Further, treatment reduced the likelihood of 0.3 mm of growth during Years 1–3 by 95%. Therefore, three different analysis approaches comparing treated growth in millimetres to a virtual control, comparing growth in millimetres to age-matched emmetropic eyes and comparing time to reach a criterion growth for treated and untreated eyes all offer an opportunity to quantify the accumulated treatment efficacy over 6 years in the absence of a concurrent control during the last 3 years of the study.

Numerous arguments have been made as to which is the best way to characterise myopia treatment effects.[15,30] One can describe a treatment effect in absolute measured units (mm, dioptres and months) or when scaled as a proportion or percentage of untreated growth. Each of the three methods used in the current analysis identified a different percentage efficacy value: slowing by 50%–60% of age-matched myopic axial length growth; slowing by almost 100% of the extra (non-emmetropic) axial length growth and increasing time to reach a criterion growth by between 2.3 and 2.8 times. Emphasising that myopia control treatment can slow axial length growth to levels seen in non-myopic eyes may be easily interpretable and familiar to those who have used population-based growth charts to compare their children to national averages.[32]

CONCLUSIONS

Over the initial 3 years during which a concurrent control was available, eyes treated with the dual focus MiSight 1 day myopia control contact lens experienced 0.37 mm of slower growth (Approach 1). Employing virtual controls of untreated myopic eyes revealed an accumulated treatment effect of 0.52 mm after 6 years of treatment (2). At all study years, treated eyes generally grew at rates expected of age-matched emmetropic eyes (3). By employing a time to reach a criterion growth as an alternative measure of treatment efficacy, the dual focus treatment delayed growth by up to 47 months, and a survival analysis indicated a 95% reduction in the chance of 0.3-mm growth over 3 years of treatment with the dual focus lens (4).

AUTHOR CONTRIBUTIONS

Paul Chamberlain: Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); visualization (equal); writing – original draft (lead); writing – review and editing (equal). **David Scott Hammond:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (supporting); writing – review and editing (equal). **Baskar Arumugam:** Conceptualization (equal); investigation (equal); methodology (equal); resources (equal); validation (equal); visualization (equal); writing – original draft (supporting); writing – review and editing (equal). **Arthur Bradley:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (lead); writing – original draft (lead); writing – review and editing (equal).

CONFLICT OF INTEREST STATEMENT

All authors are employees of the sponsor, Cooper Vision. The sponsor participated in study design, analysis, and interpretation. The authors were responsible for the preparation of this article and the decision to submit this article for publication. The lead author affirms that the article is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. All additional authors have critically contributed and reviewed the article for important intellectual content.

ORCID

David Scott Hammond https://orcid.org/0000-0002-8093-1555
Paul Chamberlain https://orcid.org/0000-0002-9082-602X

REFERENCES

1. Grosvenor T, Goss DA. Role of the cornea in emmetropia and myopia. *Optom Vis Sci*. 1998;75:132–45.
2. Jong M, Sankaridurg P, Naduvilath TJ, Li W, He M. The relationship between progression in axial length/corneal radius of curvature ratio and spherical equivalent refractive error in myopia. *Optom Vis Sci*. 2018;95:921–9.
3. Jung SK, Lee JH, Kakizaki H, Jee D. Prevalence of myopia and its association with body stature and educational level in 19-year-old male conscripts in Seoul, South Korea. *Invest Ophthalmol Vis Sci*. 2012;53:5579–83.
4. Lin LL, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore*. 2004;33:27–33.
5. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036–42.
6. Bullimore MA, Brennan NA. Myopia: an ounce of prevention is worth a pound of cure. *Ophthalmic Physiol Opt*. 2022;43:116–21.
7. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. 2012;31:622–60.
8. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036–42.
9. Manoharan MK, Thakur S, Dellhi S, Verkicharla PK. Factors associated with reduced visual acuity in myopes with and without ocular pathologies after optical correction. *Ophthalmic Physiol Opt*. 2023;43:141–9.
10. Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young G. A 3-year randomized clinical trial of MiSight lenses for myopia control. *Optom Vis Sci*. 2019;96:556–67.
11. Lam CSY, Tang WC, Qi H, Radhakrishnan H, Hasegawa K, To CH, et al. Effect of defocus incorporated multiple segments spectacle lens wear on visual function in myopic Chinese children. *Transl Vis Sci Technol*. 2020;9:11. https://doi.org/10.1167/tvst.9.9.11

12. Walline JJ, Walker MK, Mutti DO, Jones-Jordan LA, Sinnott LT, Giannoni AG, et al. Effect of high add power, medium add power, or single-vision contact lenses on myopia progression in children: the BLINK randomized clinical trial. *JAMA*. 2020;324:571–80.
13. Bullimore MA, Brennan NA, Flitcroft DI. The future of clinical trials of myopia control. *Ophthalmic Physiol Opt*. 2023;43:525–33.
14. Sankaridurg P, Weng R, Tran H, Spiegel DP, Drobe B, Ha T, et al. Spectacle lenses with highly aspherical lenslets for slowing myopia: a randomized, double-blind, cross-over clinical trial: parts of these data were presented as a poster at the Annual Research in Vision and Ophthalmology meeting, 2022. *Am J Ophthalmol*. 2023;247:18–24.
15. Chamberlain P, Bradley A, Arumugam B, Hammond D, McNally J, Logan NS, et al. Long-term effect of dual-focus contact lenses on myopia progression in children: a 6-year multicenter clinical trial. *Optom Vis Sci*. 2022;99:204–12.
16. Sankaridurg P, Bakaraju RC, Naduvilath T, Chen X, Weng R, Tilia D, et al. Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. *Ophthalmic Physiol Opt*. 2019;39:294–307.
17. Jones LA, Mitchell GL, Mutti DO, Hayes JR, Moeschberger ML, Zadnik K. Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci*. 2005;46:2317–27.
18. Rozema J, Dankert S, Iribarren R. Emmetropization and nonmyopic eye growth. *Surv Ophthalmol*. 2023;68:759–83.
19. Shamp W, Brennan NA, Bullimore MA, Cheng X, Maynes E. Influence of age and race on axial elongation in myopic children. *Invest Ophthalmol Vis Sci*. 2022;63:ARVO E-Abstract 257.
20. Chamberlain P, de la Lazon Jara P, Arumugam B, Bullimore MA. Axial length targets for myopia control. *Ophthalmic Physiol Opt*. 2021;41:523–31.
21. Lam CS, Tang WC, Lee PH, Zhang HY, Qi H, Hasegawa K, et al. 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*. 2022;106:1110–4.
22. Hammond D, Chamberlain P, Arumugam B, Bradley A. Eye growth of children undergoing myopia control treatment compared with emmetropic eye growth. [Augenwachstum von Kindern, die sich einer Myopiekontrollbehandlung unterziehen, im Vergleich zu emmetropischem Augenwachstum]. *Ophthalmologie*. 2022;119(Suppl 2):147–8.
23. Kaymak H, Graff B, Neller K, Langenbucher A, Seitz B, Schwahn H. Myopia treatment and prophylaxis with defocus incorporated multiple segments spectacle lenses. [Myopietherapie und Prophylaxe mit "Defocus Incorporated Multiple Segments"-Brillenglasern]. *Ophthalmologe*. 2021;118:1280–6.
24. Chua SY, Sabanayagam C, Cheung YB, Chia A, Valenzuela RK, Tan D, et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt*. 2016;36:388–94.
25. Comet-Group. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). *Invest Ophthalmol Vis Sci*. 2013;54:7871–84.
26. Qin Z, Peng T, Zhang Z, Lou J, Wang C, Deng R, et al. Myopia progression and stabilization in school-aged children with single-vision lenses. *Acta Ophthalmol*. 2022;100:e950–6.
27. Schober P, Vetter TR. Survival analysis and interpretation of time-to-event data: the tortoise and the hare. *Anesth Analg*. 2018;127:792–8.
28. Bullimore MA, Brennan NA, Flitcroft DI. The future of clinical trials of myopia control. *Ophthalmic Physiol Opt*. 2023;43:525–33.
29. Lam CSY, Tang WC, Zhang HY, Lee PH, Tse DYY, Qi H, et al. Long-term myopia control effect and safety in children wearing DIMS spectacle lenses for 6 years. *Sci Rep*. 2023;13:5475. https://doi.org/10.1038/s41598-023-32700-7
30. Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res*. 2021;83:100923. https://doi.org/10.1016/j.preteyeres.2020.100923
31. Mutti DO, Sinnott LT, Zadnik K, BIBS Study Group, The CLEERE Study Group. Compensation for vitreous chamber elongation in infancy and childhood. *Optom Vis Sci*. 2023;100:43–51.
32. Flitcroft DI, Loughman J, Arumugam B, Bradley A, Chamberlain P. Centile-based analysis of refractive development in the MiSight® 1 day Myopia Control trial. *Invest Ophthalmol Vis Sci*. 2020;61:ARVO E-Abstract 1372.

How to cite this article: Chamberlain P, Hammond DS, Arumugam B, Bradley A. Six-year cumulative treatment effect and treatment efficacy of a dual focus myopia control contact lens. *Ophthalmic Physiol Opt*. 2024;44:199–205. https://doi.org/10.1111/opo.13240

CHAPTER 7:QUANTIFYING TREATMENT DOSE IN INDIVIDUAL EYES

7.1. Motivations for measurement of refractive state in clinical trials

Most of the myopia progression data presented in clinical trials, including across this thesis, whether expressed in refractive error or axial elongation, is derived from aggregated, cohort averages. In other words, studies typically report the efficacy of an intervention as a single mean value for the entire treated group. However, as treatments based on inducing myopic defocus become more widely implemented in clinical practice, eye care practitioners are increasingly required to assess and discuss expectations for treatment efficacy of individual patients.

The data from the MiSight clinical trial clearly demonstrate that axial growths and myopia progressions during treatment vary enormously from eye to eye (e.g. Chapter 3, Figure 2; Figure 3,(Chamberlain, Peixoto-de-Matos et al. 2019), Figure 4,(Chamberlain, Bradley et al. 2022)) shows that the variability in axial growth of treated eyes is associated with the pre-treatment eye growth, which in turn is affected by age and other demographic factors (e.g. gender, and ethnicity), as well as environmental influences (for example, whether a patient lives in an urban or rural setting). There are also additional, perhaps unmeasured, factors unique to each patient and their living environment that may influence the rate of eye growth and progression such as after-school tutoring and reading. (Peng, Zhang et al. 2023) Beyond these patient-specific characteristics, variability can exist in the actual treatment dose delivered to each eye. The current chapter explores treatment dose delivered by MiSight 1-day lenses to children participating the MiSight clinical trial.

Factors such as how well the treatment optics are centered relative to the pupil, (Walther, Meyer et al. 2024) variations in pupil size under different lighting conditions, (Winn, Whitaker et al. 1994) accommodative response in myopes (Nakatsuka, Hasebe et al. 2005, Mutti, Mitchell et al. 2006) and particularly myopic eyes wearing the treatment contact lens, (Cheng, Xu et al. 2019) and also the inherent shape of the posterior globe can all influence the actual level of defocus that reaches the retinal image. (Pope, Verkicharla et al. 2017) Even though the lens design (such as the MiSight design described in Chapter 2) incorporates approximately +2.00 diopters of additional positive power distributed in annular treatment zones—intended to produce a consistent myopic defocus signal across a range of pupil sizes—the actual defocus “dose” that each individual eye receives can vary with the above-mentioned factors.

Studies of macaque monkeys have led to the conclusion that the peripheral or non-foveal retina plays a key role in regulating eye growth (Smith, Kee et al. 2005, Smith, Arumugam et al. 2020) which has led to studies of peripheral optics and refractive states in human myopic eyes. (Verkicharla, Mathur et al. 2012, Atchison and Rosén 2016, Zheleznyak, Barbot et al. 2016) Efforts to understand the role of peripheral optics in myopia development and myopia control have focused on measuring relative peripheral refraction, comparing the refractive state in the periphery with that at the fovea. (Mutti, Sholtz et al. 2000, Mutti, Hayes et al. 2007, Mutti, Sinnott et al. 2011) A number of studies have proposed that chronic exposure of the peripheral retina to hyperopic defocus (relative peripheral hyperopia) may be a key driver for myopia onset and progression, (Mutti, Hayes et al. 2007, Charman and Radhakrishnan 2010, Atchison and Rosén 2016) which in turn has led to the hypothesis that controlling myopia might be achieved by eliminating or even reversing this peripheral hyperopic defocus. In clinical trials, instruments such as the Grand Seiko open field autorefractor have been used to quantify the combined refractive effect of the eye plus the contact lens. (Fedtke, Ehrmann et al. 2009, Berntsen and Kramer 2013, Hair, Steffensen et al. 2021) However, these instruments only provide a single measurement value—usually taken from a small central region of the pupil (approximately 2.3 mm in diameter. (Altoaimi, Kollbaum et al. 2018) With the addition of multifocal or zonal contact lenses, the refractive state can vary considerably across the pupil. (Sah, Jaskulski et al. 2022) This variation is compounded by off-axis aberrations (such as coma and astigmatism) (Escudero-Sanz and Navarro 1999, Mathur, Atchison et al. 2008) and by the cosine compression of the pupil in the periphery, which further

distorts the refractive measurement. (Mathur, Gehrmann et al. 2013) Moreover, when a zonal multifocal lens is used, the axial separation between the lens and the eye introduces a significant parallax effect, making peripheral measurements even more challenging, this situation can be starkly illustrated in the example of artificial small pupils inlaid into the cornea where these effects are most pronounced. (Langenbucher, Goebels et al. 2013, Atchison, Blazaki et al. 2016) These examples illustrate the unsuitability of employing basic autorefractor measures to measure the refractive states of individual eyes fit with the dual focus MiSight lenses, especially when considering non-foveal refractive assessment.

A second factor that may be generating chronic hyperopic defocus stems from the indoor and close-proximity environments experienced by modern children, which are considered a significant risk factor for development and progression of myopia. (Flitcroft 2012) Because of the near proximity of indoor stimuli, young eyes will be chronically accommodating to achieve approximate focus. However, accommodative lags are routinely observed in children and can be larger in myopic eyes. (Nakatsuka, Hasebe et al. 2005, Mutti, Mitchell et al. 2006, Cheng, Xu et al. 2019) The presence and magnitude of hyperopic defocus experienced during near vision may also be affected by a myopia control treatment optic (e.g. MiSight), although data from eyes not undergoing myopia control treatment suggest that the dual focus optics of MiSight have little effect on accommodative accuracy. (Altoaimi, Kollbaum et al. 2018, Sah, Jaskulski et al. 2022) If accommodative lags are of equal magnitude to the treatment optic add powers, the near viewing treated eyes will not be exposed to myopic defocus, but instead have added hyperopic defocus.

7.2. Establishing instrumentation for measurement of complex optical designs

Recognizing the potential risks of eye globe shape and accommodative lags to the treatment strategy of delivering significant amounts of myopically defocused light to the retina, the CVI team in collaboration with Aston University in the UK and Indiana University in the US sought to examine the amount of myopic defocus (and in parallel any decrease in hyperopic defocus) present in eyes being treated with MiSight. This chapter 7 of the thesis describes one part of this study in which we monitored refractive states of 17 MiSight study subjects at each location of their pupils as they accommodated to targets over a wide range of distances. The peripheral retina measurements and analysis are complete but have not yet been published.

To better capture the optical impact of dual focus lenses, we identified a novel pyramidal wavefront sensor aberrometer—the Osiris aberrometer—developed by Costruzione Strumenti Oftalmici in Firenze, Italy. This instrument features a high sampling density (with a sampling size of just 41 μm), which allows it to measure the wavefront slope at many points across the pupil, thus can be ideally suited to measure refractive state locally within any region of a multizone lens. (Sah, Jaskulski et al. 2022, Sah, Meyer et al. 2023) Unlike traditional autorefractors that deliver a single refractive value, the Osiris aberrometer is capable of mapping the detailed distribution of refractive errors across both central and peripheral regions of the pupil. After validating the Osiris device for measuring both lower order and higher order aberrations (Singh, Jaskulski et al. 2019) an identical instrument was installed at the Aston University School of Optometry lab. The core aberrometry data were exported to our research partner at Indiana University to extract refractive state and defocus (refractive state – target vergence) maps of the pupil of eyes who participated in the six-year MiSight trial. From these defocus maps, the amount of myopic defocus was quantified and considered as a measure of treatment “dose”. Could these measurements reveal that some patients might receive a “stronger” myopic defocus dose than others, ultimately influencing treatment efficacy?

To summarize, the journey from a population-based average efficacy to understanding individual treatment responses in myopia control is complex. Not only do inherent demographic, genetic, and environmental factors contribute to variability in eye growth, but so does the intricacy of how a multifocal treatment contact lens interacts with each individual’s

ocular optics and affects the treatment dose. Advanced measurement techniques, such as those provided by the Osiris aberrometer, offer a promising pathway to accurately map the spatial distribution of refractive error across the pupil. This, in turn, allows clinicians to better understand the “dose” of myopic defocus each patient receives and to tailor treatment approaches accordingly. Ultimately, as we refine these optical measurement methods and integrate them with our understanding of individual accommodative behavior, we may move closer to personalized myopia control strategies that address the unique optical and physiological profile of each patient’s eye.

7.3. Publication: Myopia Control Dose Delivered to Treated Eyes by a Dual-focus Myopia-control Contact Lens

ORIGINAL INVESTIGATION

Myopia Control Dose Delivered to Treated Eyes by a Dual-focus Myopia-control Contact Lens

Viswanathan Ramasubramanian, BSOptom, PhD, FAAO[1]* Nicola S. Logan, PhD,[2] Susie Jones, PhD,[2] Dawn Meyer, OD,[1] Matt Jaskulski, PhD,[1] Martin Rickert, PhD,[1] Paul Chamberlain, BSc,[3] Baskar Arumugam, PhD,[3] Arthur Bradley, PhD,[3] and Pete S. Kollbaum, OD, PhD, FAAO[1]

SIGNIFICANCE: Consistent with closed-loop models of regulated eye growth, a successful dual-focus (DF) myopia-control contact lens focused a significant proportion of light anterior to the central retina in eyes of treated children viewing near and distant targets.

PURPOSE: This study examined the optical impact of a DF contact lens during near viewing in a sample of habitual DF lens wearing children.

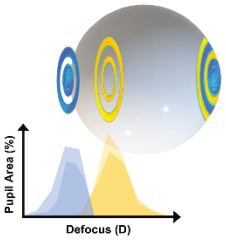
METHODS: Seventeen myopic children aged 14 to 18 years who had completed 3 or 6 years of treatment with a DF contact lens (MiSight 1 Day; CooperVision, Inc., San Ramon, CA) were recruited and fit bilaterally with the DF and a single-vision (Proclear 1 Day; CooperVision, Inc.) contact lens. Right eye wavefronts were measured using a pyramidal aberrometer (Osiris; CSO, Florence, Italy) while children accommodated binocularly to high-contrast letter stimuli at five target vergences. Wavefront error data were used to compute pupil maps of refractive state.

RESULTS: During near viewing, children wearing single-vision lenses accommodated on average to achieve approximate focus in the pupil center but, because of combined accommodative lag and negative spherical aberration, experienced up to 2.00 D of hyperopic defocus in the pupil margins. With DF lenses, children accommodated similarly achieving approximate focus in the pupil center. When viewing three near distances (0.48, 0.31, and 0.23 m), the added +2.00 D within the DF lens treatment optics shifted the mean defocus from +0.75 to −1.00 D. The DF lens reduced the percentage of hyperopic defocus (≥+0.75 D) in the retinal image from 52 to 25% over these target distances, leading to an increase in myopic defocus (≤−0.50 D) from 17 to 42%.

CONCLUSIONS: The DF contact lens did not alter the accommodative behavior of children. The treatment optics introduced myopic defocus and decreased the amount of hyperopically defocused light in the retinal image.

Optom Vis Sci 2023;100:376–387. doi:10.1097/OPX.0000000000002021

OPEN



Author Affiliations:
[1]School of Optometry, Indiana University Bloomington, Bloomington, Indiana
[2]School of Optometry, Aston University, Birmingham, United Kingdom
[3]CooperVision Inc., Pleasanton, California
*viswa.ramasubramanian@gmail.com

In response to the high prevalence of myopia in young adults,[1] approaching 100% in certain demographics,[2,3] research efforts have sought to slow or stop the accelerated growth of young eyes.[4] A longer eye is associated with sight-threatening retinal pathologies[5–8] in later years. Most extant methods at the time of writing use various optical strategies to alter the retinal image in progressing myopic eyes.[9–12] Spectacle lenses containing central clear zones surrounded by either groups of plus powered small lenslets[10,13,14] or arrays of scatter sources[15] have demonstrated some efficacy at slowing myopia progression. Repurposed presbyopic multifocal contact lens designs[9,16,17] have generally proven less effective than a novel dual-focus contact lens[11] specifically designed for myopia control, which received U.S. Food and Drug Administration approval in the United States in 2019.[18] MiSight 1 Day (omafilcon A; CooperVision, San Ramon, CA; coopervision.com) soft (hydrophilic) contact lenses with dual-focus optics were approved by the U.S. Food and Drug Administration for daily wear and are indicated for the correction of myopic ametropia and for slowing the progression of myopia in children with nondiseased eyes, who at the initiation of treatment are 8 to 12 years of age and have a refraction of −0.75 to −4.00 D (spherical equivalent) with ≤0.75 D of astigmatism. The lens is to be discarded after each removal.

One type of myopia control intervention includes optical features designed to focus some proportion (e.g., 25 to 50%) of the light anterior to the retina. The resulting myopic defocus has been shown to attenuate or prevent the eye elongation induced by simultaneously present hyperopic defocus in model work.[19,20] Published data show that the small lenslets included in the Defocus Incorporated Multiple Segments spectacle lenses (MiYOSMART; Hoya Vision Care, Tokyo, Japan) have approximately +3.50 D of added power,[10,13] whereas the dual-focus contact lens (MiSight 1 Day) includes annular zones containing approximately +2.00 D of added power.[21] Missing from these descriptions of the lenses themselves is a quantification of the myopic defocus dose delivered to the myopic child's retina. This distinction is important because the ability for a myopia control intervention to deliver myopic defocus depends on the eye's optics and the lens' treatment zone design. Said another way, just because a lens has a zone or zones of +2.00 or +3.50 D, this does not mean this is the amount of myopic defocus that is introduced by the lenses when worn. Two key

parameters of the eye's optics will dominate the resultant defocus present at the retina. First and most significant is the accommodative response,[22] which is known to lag at near in most eyes and can lag more in some eyes than others,[21] potentially being larger in myopic eyes.[23,24] Accommodative lags will generate hyperopic defocus in the retinal image. Increased lags in myopic eyes wearing multifocal contact lenses have been reported,[25] which can become amplified after sustained use of the multifocal lenses.[16] Also, negative spherical aberration found in accommodating eyes[26–28] generates a hyperopic shift in refractive error with increasing distance from the pupil center.[29] For example, young accommodating eyes may have sufficient negative spherical aberration to counteract positive spherical aberration introduced in a contact lens,[30] which may explain the low impact of presbyopic contact lens designs when implemented as myopia control therapy.[16]

Model work has shown that the magnitude of introduced defocus will regulate eye growth[31–33] and the proportion of defocused light introduced to the retina.[34] Also, in the presence of a grow signal, studies have shown that more diopters of plus defocus[35] and a greater proportion of myopically defocused light[20,36] can both amplify the slowing effect of this optical treatment strategy. The present article sought to quantify the myopic defocus dose delivered and the associated reduction in hyperopically defocused light by the treatment optics of a dual-focus contact lens to the retina of children undergoing myopia control therapy.

Because the treatment optics of this contact lens are restricted to two narrow annuli, assessing the refractive impact of such lens designs with instruments that integrate over some device-determined region of the pupil cannot capture the zone-specific refractive impact.[37,38] Spatially resolved aberrometers, however, are ideally suited for this task in that they measure wavefront slope at many hundreds of locations in the pupil from which local refractive states can be calculated.[13] Introduced myopic defocus and reduced hyperopic defocus produced by the treatment optics can be quantified by assessing the refractive state in the geographic regions of the pupil covered by the treatment optic. Examining the full pupil, the same aberrometry data can be used to quantify increases in the proportion of myopically defocused light and decreases in the proportion of hyperopically defocused light in the retinal image.[31,32,34] Because of the success of the dual-focus contact lenses in slowing rate of myopia progression,[11,39,40] it was hypothesized that the dual-focus contact lens can consistently (*a*) deliver a significant dose of myopic defocus over a wide range of viewing distances in the eyes of treated myopic children and (*b*) decrease the amount of hyperopically defocused light in the retinal image.

METHODS

Subjects

Seventeen adolescent children aged 14 to 18 years (mean standard deviation [SD] age, 16.61 [1.63] years) and having completed either 3 or 6 years of myopia control therapy[40] with dual-focus soft contact lenses (MiSight 1 Day) were tested at the Aston University (United Kingdom) research clinic during their final year of treatment. This research was reviewed by the Aston University Research Ethics board and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research. Written informed consent or assent occurred with each participant as age-appropriate (and guardian consent where applicable) before entering in the aberrometry substudy. During the test visit, optical measurements were acquired from the right eye while children wore their dual-focus treatment lenses in both eyes. Subsequently, children wore matched power single-vision lenses (Proclear 1 Day; CooperVision) of the same distance prescription in both eyes with approximately 15 minutes of adaptation period before optical measurements of their right eyes. All participants were experienced and well-adapted contact lens wearers. No adaptation problems were reported. As previously published,[11] distance visual acuity was similar with both single-vision and dual-focus contact lenses. This study design allowed direct comparison of the optical impact of dual-focus and single-vision lenses on the central retinal images of right eyes while binocularly viewing stimuli over a wide range of distances. Both lenses shared the same base curve (8.7 mm), diameter (14.2 mm), and material (omafilcon A). The single-vision lenses use an aspherical front surface to avoid power variations in spherical aberration,[41] and the dual-focus lenses use a four-zone concentric design[42] with two zones (center zone and ring 2 [R2]) designed to correct the refractive myopia and two annular zones (ring 1 [R1] and ring 3 [R3]) identified as treatment zones with added plus power to generate myopic defocus at the retina. Eyes were fitted with lenses to optimize distance visual acuity using a maximum plus refraction technique.

Ex Vivo Contact Lens Aberrometry

Maps of optical power (Figs. 1A, B) across two sample −1.00 D lenses (single-vision and dual-focus) were measured *ex vivo* using a previously validated[43] single-pass Shack-Hartmann aberrometer (ClearWave; Lumetrics, Inc., Rochester, NY) with a sampling resolution of 104 µm. Distributions of sampled power (Fig. 1D) were plotted for each refractive correction zone (center zone and R2 of the dual-focus lens) and the two treatment zones (R1 and R3 of the dual-focus lens). To allow direct comparison between the two lenses, the same calculations were performed for the single-vision lens using identical regions of the measured wavefront (Fig. 1C). Average powers in the center zone of both lenses were within 0.02 D of the labeled −1.00 D power. The average added powers in the two treatment zones of the dual-focus lens were +2.00 and +2.25 D for R1 and R3, respectively. The increase in plus power within R3 is consistent with a small amount of positive spherical aberration. Conversely, the outer analysis zones of the single-vision lens have more negative power because of negative spherical aberration in this lens.[41]

Optical Measurements

A validated[44] double-pass pyramidal wavefront sensor (Osiris; CSO, Florence, Italy) was used to measure (sampling resolution of 41 µm) the wavefront exiting the right eye as children binocularly accommodated to high-contrast stimuli at distances of 3.98, 0.98, 0.48, 0.31, and 0.23 m (target vergence [D], of −0.25, −1.02, −2.08, −3.23, and −4.35 D). At 3.98 m, children viewed the 0.30 logMAR line on an illuminated Early Treatment Diabetic Retinopathy Study chart. At near viewing distances, the stimuli were changing sequences of high-contrast letters (0.30 logMAR equivalent) displayed on an iPhone 6 (Apple, Cupertino, CA) with the screen luminance of 150 cd/m^2. Room illumination during measurements was 6 lux. Head position was stabilized with both chin and forehead rests. The instrument measurement axis was aligned with the eye's primary line of sight. Therefore, when children accommodated binocularly to near stimuli, the left eye converged to maintain fixation, whereas the relative position of the right remained approximately constant throughout the experiment.

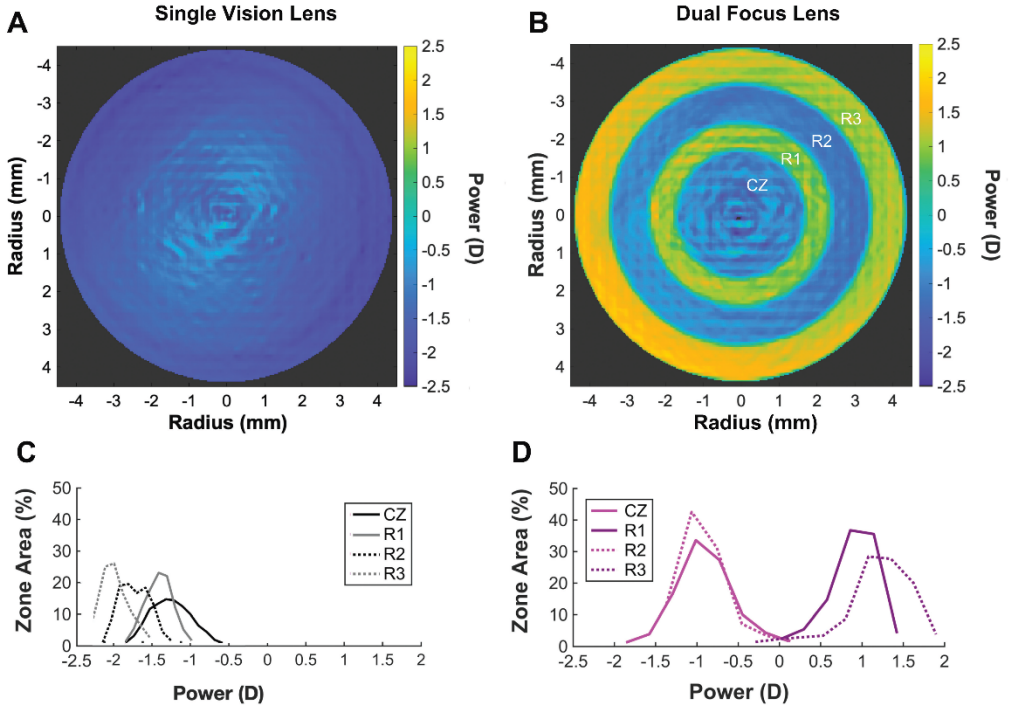


FIGURE 1. Off-eye optical design of the single-vision and dual-focus lenses. Measured (ClearWave; Lumetrics, lumetrics.com) power maps for two sample contact lenses (single-vision (A) and dual-focus (B)) with labeled power –1.00 D from which zone-specific power distributions (C, D) were derived. Rings on the single-vision power map (A) mirror the zone boundaries observed in the dual-focus lens (B). Power distributions (C, D) characterize each of the four zones, quantified using bin widths of 0.25 D.

Before each measurement, children were instructed to blink twice and keep the letters as clear as they could. Three repeats of good quality data were acquired at each stimuli position.

Data Analysis

Osiris wavefront error maps were imported into MATLAB (MathWorks, Natick, MA), and custom software (Indiana Wavefront Analyzer; MAPLE, Bloomington, IN) was used to compute local measures of refractive state in the pupil (natural pupil size) using the slope/radial distance equation.[38] The coordinate center was aligned with the contact lens center. Corrected refractive state maps were subdivided into geometric zones that matched the measured geometry of the dual-focus contact lens allowing a zone-specific assessment of the refractive impact of the dual-focus lenses. Data sets corrupted because of blinks, eye lashes, tear breakup, and momentary lapses of gaze and/or accommodation were manually excluded. Data cleaning used thresholding (exclude values <5% of the mode) and removal of local samples corrupted at pupil margins. Refractive states from cleaned data repeats were used to plot pooled refractive state histograms with bin width of 0.25 D for both dual-focus and single-vision lenses. In Fig. 2, the "repeat 1" data contain 29,422 measures of refractive states in the pupil (center zone, 5660; R1, 5623; R2, 11,213; and R3, 6926). Therefore, when three repeat measurements are pooled, the histograms reveal the distribution of approximately 88,266 refractive states (center zone, 16,980; R1, 16,869; R2, 33,639; and R3, 20,778) sampled across the pupil. The data processing sequence is shown with examples in Fig. 2.

From the pooled refractive state histograms, corresponding target vergence (–1/target distance in meters) was subtracted to yield pooled defocus histograms. Defocus (refractive state – target vergence) histograms across the full pupil were weighted by the Stiles-Crawford effect ($\sigma = 0.115$)[45] and were used to quantify the proportion of hyperopic (positive) and myopic (negative) defocus and focused light present at the retina. Pooled defocus values from each histogram were used to compute the mean and SD defocus contributed by each zone.

Stiles-Crawford effect weighted area of full pupil that produced myopically and hyperopically defocused light was used to quantify the proportion of myopically and hyperopically defocused light within the retinal image. Two sets of criteria were used to define myopic, hyperopic, and focused light. The first analysis used the common clinical thresholds[46,47] for defining myopia and hyperopia (refractive state values beyond –0.50 and +0.75 D), and a second pair of refractive criteria was based on the familiar depth of focus (±0.25 D) to define focused light (Fig. 3A). The resulting three

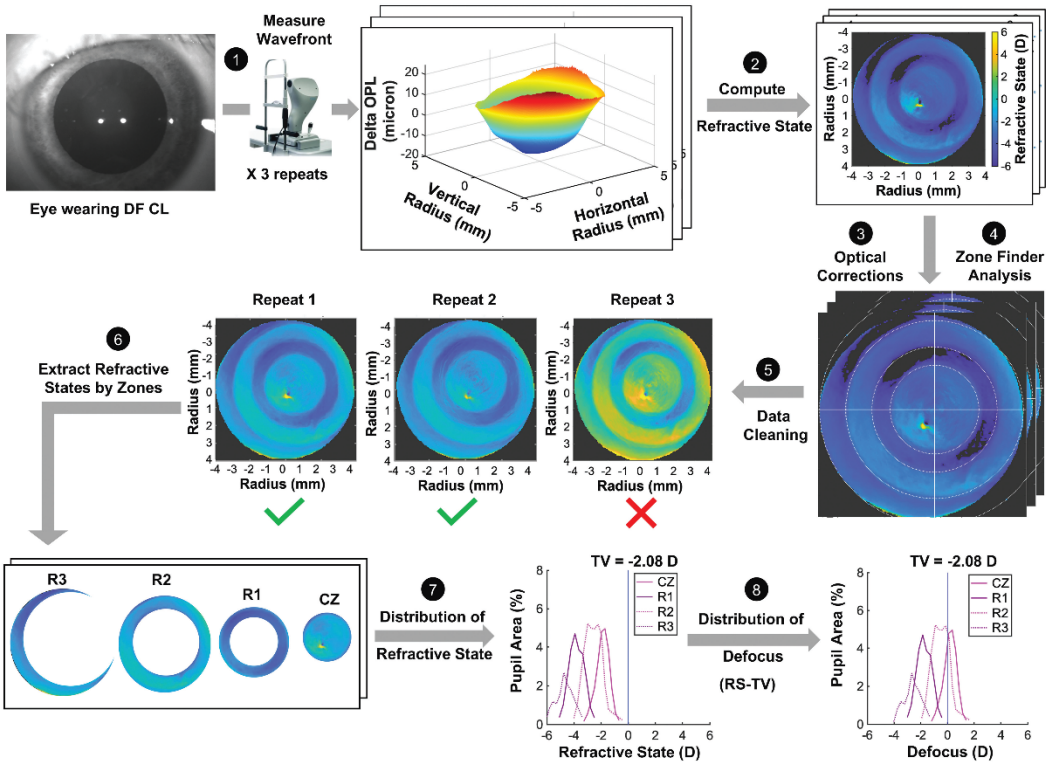


FIGURE 2. Data processing sequence with sample data starting at top left and finishing bottom right. (1) A sample anterior eye image collected from the aberrometer of an eye fit with a dual-focus CL, measured three times with the clinical Osiris aberrometer, which output three wavefront error maps. (2) Custom software implemented in MATLAB,[13] calculated the local refractive state for each sample in the wavefront revealing the expected four-annular-zone structure of the MiSight CL.[11] (3) Raw refractive state data were corrected for prism and lens centration errors, and (4) the measured zone geometry of this lens was used to locate zone boundaries in the maps. (5) In a few cases (3 of 17), it was observed that children would accommodate accurately on two of the three trials but fail to accommodate on the third. Mean data excluded the outlier data set. Also, data corrupted by blinks, lashes, and tear disruptions were excluded. (6) Refractive data from each zone (center zone and three surrounding rings, R1, R2, and R3) were isolated and (7) used to plot refractive state distributions for each individual zone. (8) Refractive state distributions were converted to defocus distributions by subtracting the target vergence (in diopters). CL = contact lens.

proportions (myopically and hyperopically defocused light and focused light) were plotted using three-axes ternary plots,[48] which revealed the proportion of each type of defocus by the position of a datum along all three axes of this triangular space. The defocus proportions are revealed by tracing each of the three colored lines that pass through a data point to the matched colored scale. The example in Fig. 3B shows a data point representing proportions of 0.3 myopic (red), 0.4 hyperopic (blue), and 0.3 focused (black) light.

RESULTS

To quantify the retinal defocus generated by each contact lens zone, the target vergence was subtracted from the measured refractive state, revealing the presence of myopically (negative valued) and hyperopically (positive valued) defocused light. On-eye defocus distributions are plotted for the full pupil (Fig. 4) and for each zone (Fig. 5, center zone, R1, R2, and R3) of a sample eye (18-year-old with a refractive error of –4.50 D in the right eye) fit with either a single-vision (top panels) or a dual-focus (bottom panels) lens for all five viewing distances (target vergences [D] of –0.25, –1.02, –2.08, –3.23, and –4.35 D). The height of each distribution at zero on the *x* axis indicated the percentage of focused light.

Center zone defocus distributions (Fig. 5) provided an indication of the accommodation accuracy, revealing low levels of myopic defocus when viewing a distant target (accommodative lead) and a gradual drift to hyperopic defocus as the target approached the eye (accommodative lag). With the single-vision lens, hyperopic defocus dominated the image generated by the two outer zones being greatest in R3, especially when the eye was accommodating (e.g., mode for R3 with –4.35 D target = +2 D). Similar trends were seen in the distance correction zone data from the same eye fit with the dual-focus lens

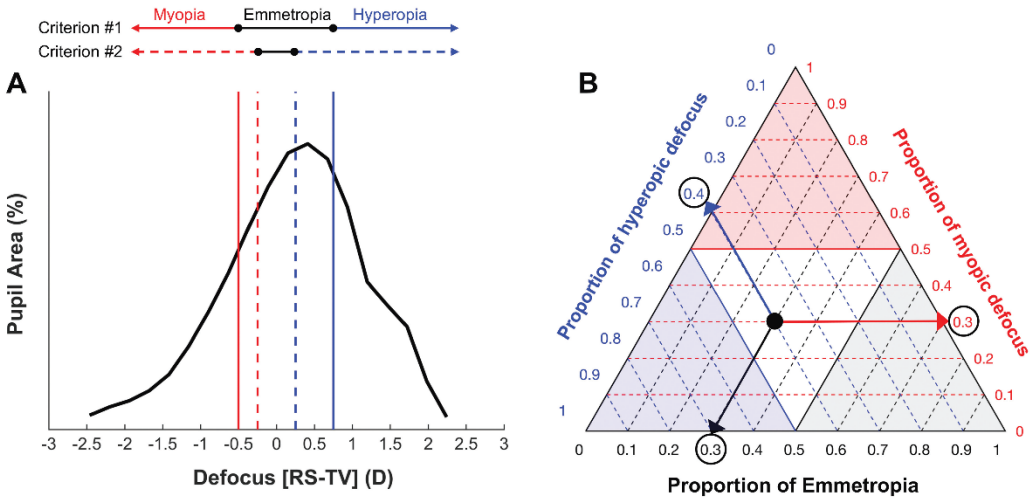


FIGURE 3. Methods used to classify the focused and defocused light in the retinal image. (A) Criteria for classifying myopically (red) and hyperopically (blue) defocused light and focused (black) light from the continuous distributions of measured retinal defocus. (B) Example ternary plot of the three dimensions of proportions of myopic, hyperopic, and focused light (red, blue, and black). Colored arrows show how proportions are determined for a given data point. Defocus = Refractive state (RS) – Target vergence (TV).

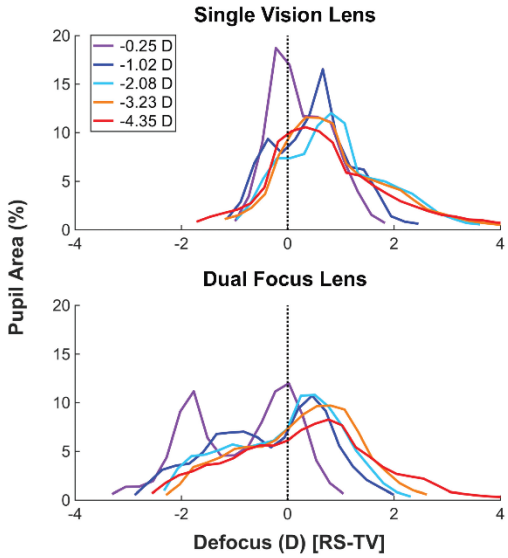


FIGURE 4. Full pupil defocus distributions from a sample eye. Defocus distributions (0.25 D bins) from the sample eye fit with the single-vision (top panel) and dual-focus (bottom panel) lenses for the full pupil. The measured refractive states were converted to defocus distributions (difference between the measured refractive state and the target vergence: defocus (diopters) = refractive state – target vergence) with positive values indicating hyperopically defocused light and negative for myopic defocus. Black dashed lines plot the position of the eye's retina where defocus is zero.

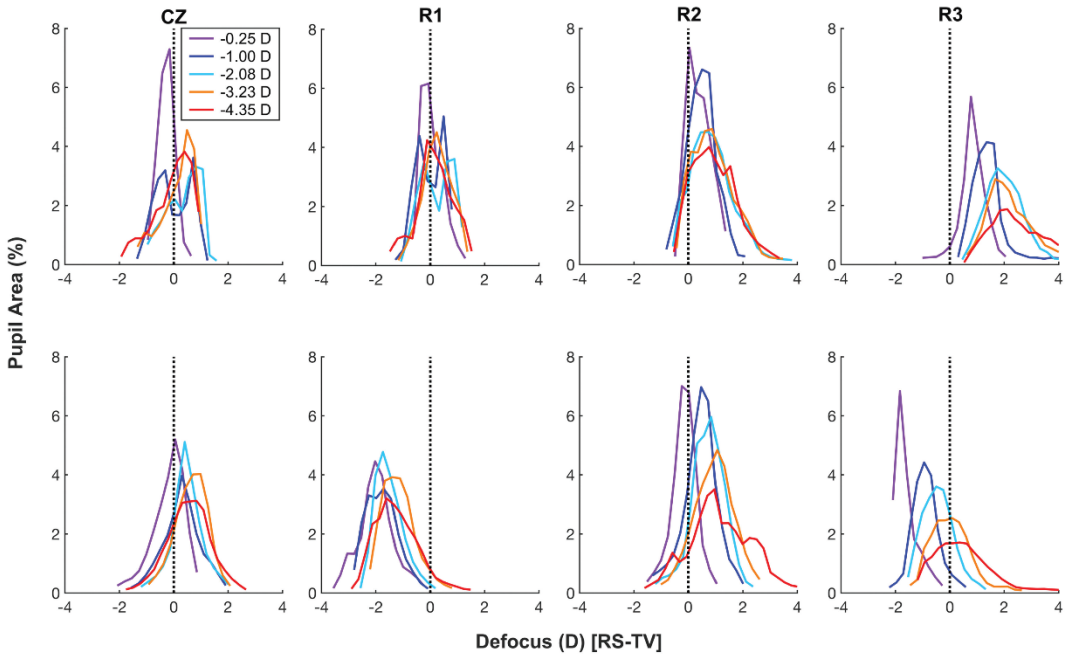


FIGURE 5. Zone-wise defocus distributions with single-vision and dual-focus lenses. Defocus distributions (0.25 D bins) for the same eye as Fig. 4, for four individual zones (two correction zones [center zone and R2] and two treatment zones [R1 and R3] for all five viewing distances). Defocus = Refractive state (RS) – Target vergence (TV).

(lower panels, center zone and R2), but the treatment zones (R1 and R3) revealed an obvious shift toward myopic defocus at all viewing distances, with defocus in R1 being almost exclusively myopic. The myopic shift observed in treatment R3 when viewing the 3.98 m target gradually shifted toward zero and included some hyperopic defocus at the nearest viewing distances (31 and 23 cm), reflecting the combined effects of accommodative lag and increased negative spherical aberration present in this young eye viewing near targets. The clear double-peaked defocus distributions created by the dual-focus lens seen in the full pupil data (Fig. 4) at the farther viewing distances (3.98 m and 98 cm) disappeared as spherical aberration levels increase with accommodation. For each lens and zone, as the target approached, the eye accommodated and the defocus distributions widened, revealing increased aberrations in this young accommodating eye. For example, the SD of the distributions for the full pupil increased from 0.81 to 1.56 D for the single-vision lens and from 1.23 to 1.54 D for the dual-focus lens, as the target approached from 3.98 m to 23 cm.

The mean defocus values from each of the four zones are plotted in Fig. 6 for each child (gray lines) and the sample mean (bold lines and symbols). Although the retinal images of individual children included slightly different levels of defocus, the central trends dominated, resulting in standard error of the mean (shown as error bars) values on the scale of the plotted symbols (average standard error of the mean, 0.20 D). The accommodative behavior of these children can be seen by examining the center zone data (Figs. 6A, B). With both single-vision and dual-focus lenses, children generally experienced small accommodative leads at distance (mean, –0.86 D for single-vision and –0.94 D for dual-focus), which transitioned to accommodative lag at near (mean, +0.59 D for single-vision and +0.98 D for dual-focus). Notably, these center zone data were almost identical for the single-vision and dual-focus lenses (mean difference, 0.14 D across all viewing distances), revealing that introduction of treatment optic zones (R1 and R3) in the dual-focus lenses did not affect the accommodative behavior. When comparing the pupil regions covered by the treatment zones (R1 and R3), defocus was consistently more myopic (R1 [dual-focus – single-vision] = –2.05 D, R3 [dual-focus – single-vision] = –2.40 D) when eyes were fit the dual-focus lens (Figs. 6C, D, G, H). The accommodative lag observed at near in the center zone data (Figs. 6A, B) steadily increased as measured farther from pupil center (R3 > R2 and R1), resulting in hyperopic defocus in eyes fit with single-vision lenses at nearest distances (mean defocus for targets 0.33 m and nearer; R1, 0.88 D; R2, 1.27 D; and R3, 1.70 D). This larger hyperopic shift at the pupil margins was caused by the well-documented increase in negative spherical aberration as the eye accommodates.[27,30] The combined accommodative lag and negative spherical aberration reduce the level of myopic defocus introduced by the treatment optics of the dual-focus lens. For example, R1 and R3 introduced –2.92 and –2.87 D of myopic defocus, respectively, at 4 m, which reduced to –0.63 and –0.27 D at 0.23 m. For stimuli beyond 0.4 m, all children experienced myopic defocus. For stimuli 0.31 m and nearer, 12 (71%) and 10 children (59%) experienced average myopic defocus in the pupil covered by R1 and R3 treatment zones, respectively.

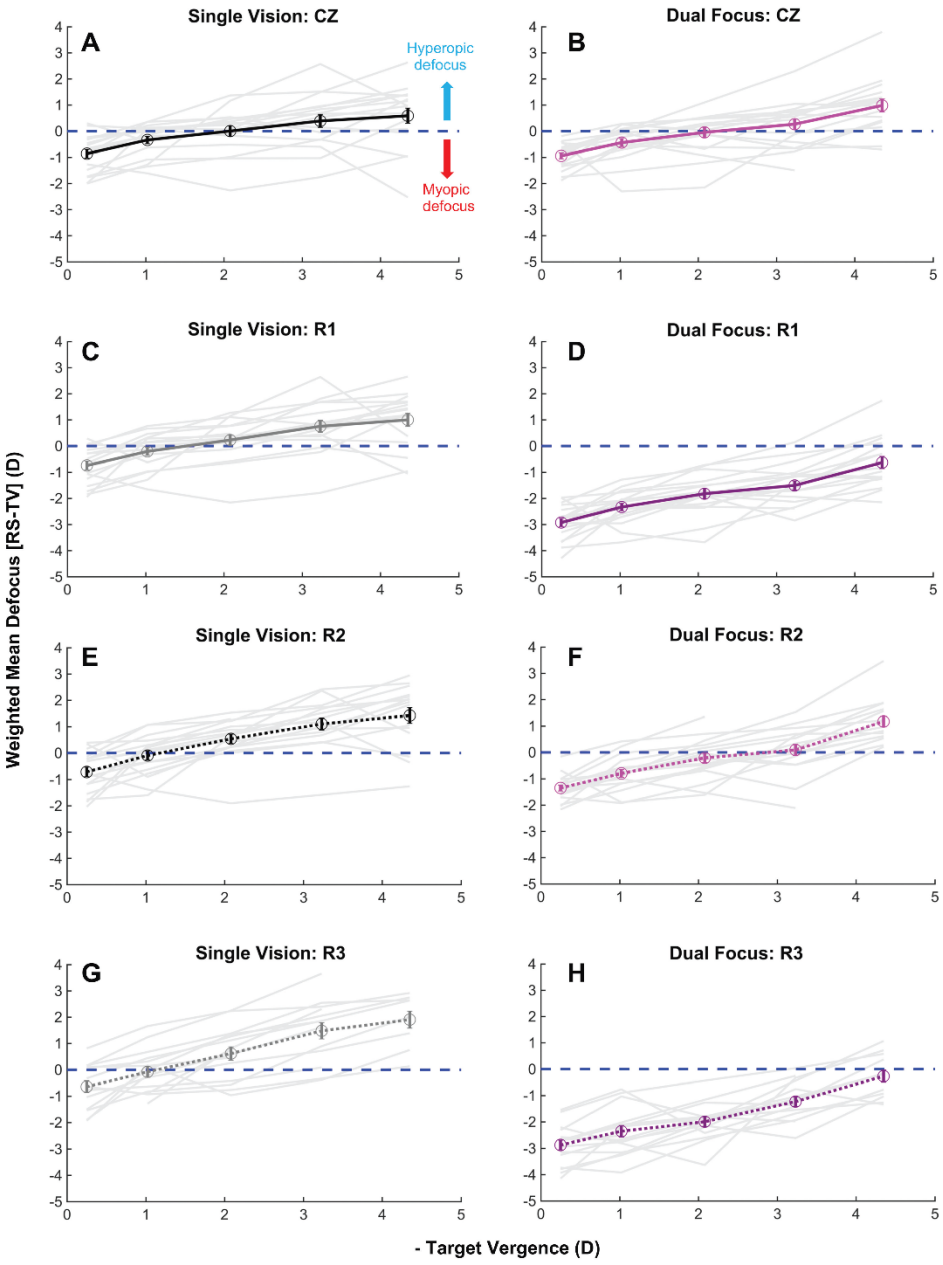


FIGURE 6. Mean defocus (defocus = refractive state – target vergence) as a function of target vergence from all children. Mean defocus values (*y* axis) observed at each target vergence (*x* axis) were plotted for each zone (center zone, R1, R2, and R3) for eyes fit with the single-vision (A, C, E, G) or the dual-focus (B, D, F, H) contact lenses. Data for each of the 17 tested eyes were plotted as gray lines, and the mean of the 17 was plotted as a bold line and symbol. Error bars were ±1 SEM. SEM = standard error of the mean.

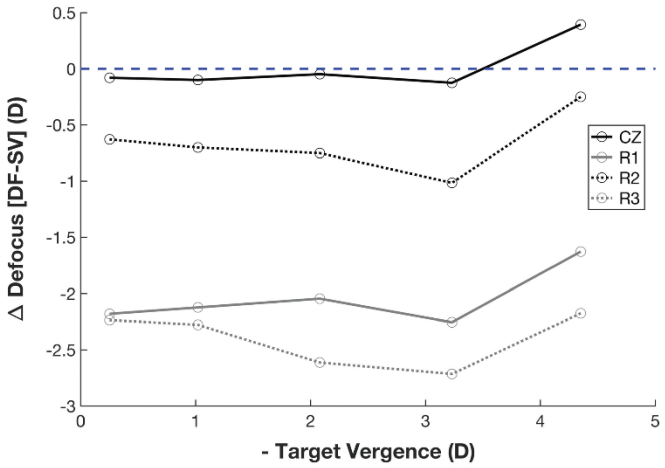


FIGURE 7. Zone-wise impact of dual-focus lens on the defocus of eyes compared with the single-vision control lens. Mean difference in defocus between the dual-focus and single-vision lens for four individual zones (two correction zones [center zone and R2] and two treatment zones [R1 and R3]) as a function of target vergence in diopters.

The impact of the treatment zones can be quantified by comparing the defocus generated by those regions of the pupil when fit with the dual-focus with the same regions of the pupil when the eye was fit with the single-vision lens. The difference in defocus between the dual-focus and single-vision lens for each zone is plotted in Fig. 7. The center correction zone generated the same levels of defocus (mean, 0.01 D), whereas, in the second correction zone (R2), on average, there was myopic defocus (mean, –0.66 D). However, when comparing regions of the pupil covered by the treatment optics (R1 and R3), the dual-focus lens created, on average, a –2.05-D myopic shift in defocus for R1 and a –2.40-D shift for R3, which varied little with viewing distance. The data in Figs. 6 and 7 show the ability of the dual-focus lens to achieve two goals, generating significant myopic defocus across the full pupil at the greater viewing distances (mean, –2.25 D between 3.98 and 0.48 m) and a combined introduction of myopic defocus (–0.91 D for distances ≤0.31 m) and removal of the significant hyperopic defocus observed in eyes fit with the single-vision lens when viewing near stimuli (mean, 1.29 D for distances ≤0.31 m).

The aforementioned analysis of the data in Figs. 6 and 7 characterizes the myopia control dose delivered by each treatment optic in units of diopters. However, it has been shown in model work[20] that the amount of myopically defocused light on the retina plays a significant role in influencing eye growth. Therefore, the next section focuses on the proportion of the light forming the retinal image, which can be considered to contribute to myopia control (increase in the proportion of myopically defocused light and reduction in the proportions of hyperopically defocused light). Central to this analysis is the underlying geometry of the dual-focus lens (Fig. 2) and the proportion of the pupil covered by each of its zones. The average percentages of the full pupil covered by each of the four zones remained relatively stable across all viewing distances because pupil size varied little with viewing distance (e.g., mean diameter was 6.57 mm when viewing a distance target and 6.34 mm when viewing a near target at 0.23 m).

Using the refractive criteria shown in Fig. 3A, the three proportions of focused and myopically and hyperopically defocused light extracted from the full pupil defocus distributions of each eye and each lens were depicted graphically in ternary plots for eyes fit with both the single-vision (Figs. 8A, C) and dual-focus (Figs. 8B, D) lenses for all viewing distances tested: 3.98 m (filled circles), 0.98 m (open circles), 0.48 m (open squares), 0.31 m (open diamonds), and 0.23 m (filled triangles). Predictably, the criterion set with the wider range for defining "focused" (–0.50 to +0.75 D) generated larger proportions of focused light (Figs. 8A, B) than the data using the narrow range (±0.25 D) plotted in Figs. 8C and D. In every case, there was a consistent drift in the data from the upper regions (red shaded) indicating retinal images dominated by myopic defocus to the lower left blue region where images were dominated by hyperopic defocus. For example, while viewing the farthest target, approximately 62 (single-vision) and 87% (dual-focus) of the full pupil was dominated by myopic defocus, which reduced to 18 (single-vision) and 27% (dual-focus) for the nearest target. Conversely, the proportion of hyperopic defocus in the retinal image increased from 10 (single-vision) and 3 (dual-focus) to 69 (single-vision) and 50% (dual-focus) for the farthest and nearest viewing distances, respectively. The bias toward myopic defocus and away from hyperopic defocus created by the dual-focus lens can be observed by comparing the locations of corresponding data in the right and left panels of Fig. 8. Although it is convenient to quantify the proportions (or percentage) of the pupil generating each type of defocus, these percent values will vary with pupil size, as shown for other lens designs with radially varying power.[49]

The treatment dose introduced by the R1 and R3 zones of the dual-focus lens can be quantified as the increase in proportion of myopically defocused light and the decrease in proportion of hyperopically defocused light in the retinal image created by the dual-focus optic; each occurs simultaneously at each viewing distance. These shifts in the proportion of myopically defocused and hyperopically defocused light were quantified and are shown in

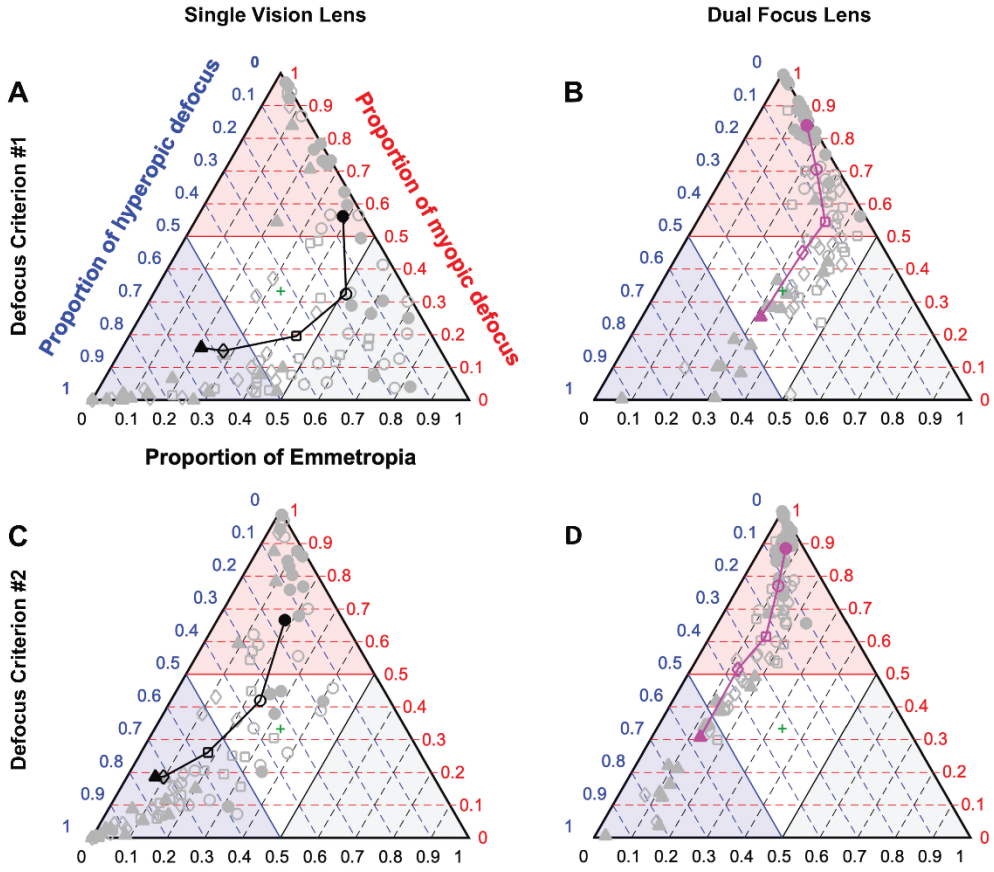


FIGURE 8. Ternary plots of focused and defocused light in the retinal image. The three proportions of focused and myopically and hyperopically defocused light forming the foveal images were extracted from the full pupil defocus distributions (Fig. 4) and plotted for each eye and each lens using three axes ternary plots. Data for eyes fit with the single-vision (A, C) and dual-focus (B, D) lenses for each viewing distance: 3.98 (filled circles), 0.98 (open circles), 0.48 (open squares), 0.31 (open diamonds), and 0.23 m (filled triangles) are plotted for the sample means (bold symbols and lines) and for each eye (low contrast gray symbols).

Table 1. Introduction of additional myopically defocused light (between 30 and 40%) dominated at the larger viewing distances, whereas reduction in the proportion of hyperopically defocused light dominated at the nearest distances. Despite the added plus power in the treatment rings, the dual-focus lens design was able to maintain similar proportion of focused light in the retinal image as the single-vision lens at each viewing distance (average, 20%).

DISCUSSION

The main purpose of this study was to quantify the myopia treatment dose delivered by a myopia control dual-focus contact lens containing two annular treatment zones, which include approximately 2.00 D of added plus power (Fig. 1). Dose was assessed along two dimensions: the diopters of defocus created in the retinal image (Figs. 4 to 7) and the proportion of myopically and hyperopically defocused light within these retinal images (Figs. 3, 8). The data summarized in this article show that, on both scales (diopters and proportion of light in the image), the dual-focus contact lens treatment optics successfully introduced an average myopia control dose of 2.00 D into the retinal image at all viewing distances. These results are consistent with the proposed closed-loop optical mechanisms by which dual-focus myopia-control contact[40] and spectacle[15] lenses achieve treatment success.

The similar defocus levels observed in pupil regions covered by the center zones (Figs. 6A, B) of both single-vision and dual-focus lenses reveal that the dual-focus optics did not disrupt normal

TABLE 1. Optical impact of dual-focus lens on the proportion of focused and defocused light in the retinal image relative to the single-vision control lens

Defocus criterion 1			
Target vergence (D)	Δ Proportion (%) of hyperopic defocus (DF-SV)	Δ Proportion (%) of myopic defocus (DF-SV)	Δ Proportion (%) of focused light (DF-SV)
−0.25	−0.04 (−4%)	0.28 (+28%)	−0.24 (−24%)
−1.02	−0.11 (−11%)	0.38 (+38%)	−0.27 (−27%)
−2.08	−0.25 (−25%)	0.35 (+35%)	−0.10 (−10%)
−3.23	−0.35 (−35%)	0.30 (+30%)	0.06 (+6%)
−4.35	−0.20 (−20%)	0.09 (+9%)	0.11 (+11%)
Defocus criterion 2			
Target vergence (D)	Δ Proportion (%) of hyperopic defocus (DF-SV)	Δ Proportion (%) of myopic defocus (DF-SV)	Δ Proportion (%) of focused light (DF-SV)
−0.25	−0.11 (−11%)	0.22 (+22%)	−0.11 (−11%)
−1.02	−0.22 (−22%)	0.35 (+35%)	−0.13 (−13%)
−2.08	−0.33 (−33%)	0.35 (+35%)	−0.03 (−3%)
−3.23	−0.35 (−35%)	0.33 (+33%)	0.03 (−3%)
−4.35	−0.17 (−17%)	0.12 (+12%)	0.05 (−5%)

Proportional changes in hyperopically defocused, myopically defocused, and focused light created by the dual-focus and the single-vision contact lenses for each target vergence and for the two refractive criteria used to segregate the defocus scale into three dimensions (proportions of focused and of myopically and hyperopically defocused light in the retinal image, see Fig. 3A). DF-SV = dual-focus–single-vision.

accommodation.[50] The leads and lags similarly contribute to the defocus levels created by the noncentral annular correction zone, but at the increased distance from the lens and pupil center of this annular zone, spherical aberrations of the contact lens and that of the eye also contribute to the resulting defocus patterns. The essentially normal accommodative behavior seen in eyes fit with the dual-focus lenses reveals that the correction zones (center zone and R2) remain the focus target for these eyes, with no evidence that children use the added plus power in the treatment zones to focus near targets. This result is crucial for such lenses to be able to deliver myopic defocus with the treatment optics.

As reported previously for adult eyes,[27,28] spherical aberration of the adolescent eyes in this study (mean age, 16.61 years) drifted negatively as the eye's lens changes shape during accommodation. Changes in spherical aberration of eyes fit with single-vision lenses were quantified with the Zernike coefficient C40 for wavefronts measured across the full pupil at each viewing distance. Average pupil diameters were 6.60, 7.05, 7.04, 6.85, and 6.34 mm for viewing distances of 3.98, 0.98, 0.48, 0.31, and 0.23 m, respectively. Although there were individual differences in absolute levels of spherical aberration, accommodation induced a negative shift in all eyes, resulting in a mean spherical aberration (eye + single-vision lens) that increased from −0.07 to −0.50 µm as the viewing distance was reduced from 3.98 to 0.23 m with a best fit slope of −0.105 µm per diopter of target vergence. Spherical aberration of eyes with dual-focus contact lens was not determined, as the Zernike polynomials cannot accurately fit the zonal power profile of this lens (Figs. 1B, D).

Because accommodation was unaffected by the dual-focus optics of the MiSight 1 Day lenses relative to single-vision lenses, ocular spherical aberration changes resulting from changing eye lens shape are matched for eyes fit with single-vision and dual-focus lenses. For this reason, the differences in average defocus of each zone between the single-vision and dual-focus lenses (Fig. 7) generally remained unchanged with target vergence. The resulting defocus differences, however, reflect radial differences in power of the two lenses. The added plus power in the dual-focus treatment zones created between −2.00 and −2.50 D of added myopic defocus and the negative spherical aberration of the single-vision lens resulted in the outer correction zone of eyes fit with the dual-focus lens (R2) being approximately −0.50 D more myopic. The increasing levels of negative spherical aberration observed in accommodating eyes resulted in increased hyperopic shifts that increased with radial distance from the pupil center (Fig. 6). The hyperopic shifts were small for distance viewing; for example, the mean shift in the outer correction ring R2 of the single-vision lens is less than 0.25 D for viewing distance of ≥1 m. However, at the closest distances, the hyperopic shifts can exceed 1.00 D at the edge of the pupils. These high levels of negative spherical aberration impact the defocus values associated with each zone.[49,51] For example, the hyperopic drift in defocus values (Fig. 6) associated with closer viewing distances (≤31 cm) is 0.49 D in the center zone of the single-vision, and this increases to 0.88 D for R1, 1.27 D for R2, and 1.70 D for R3. The extra 1.20 D of hyperopic shift observed in R3 compared with center zone is directly attributable to the changes in spherical aberration levels of the accommodating eyes.

The current study evaluated the real-world situation where contact lenses are nominally decentered on eye. The impact of contact lens movement during the interblink interval, however, was minimized with our blink-blink-capture protocol described in the methods, which, in most cases, resulted in three consistent repeat measures. Contact lens decentrations were small (0.37 mm temporally and 0.36 mm inferiorly) and had little or no effect on the proportion of light being imaged through the zones. For an average pupil size of 6.80 mm and average inferotemporal decentration of 0.37 mm, the changes in proportion of light imaged through the zones were as follows: center zone and R1, 0%; R2, −3.47%; and R3, +3.47%.

Quantifying the dose experienced in human children undergoing myopia control treatment is complicated because of the influence of accommodative responses, variability in pupil size (mean SD, 0.80 mm), and levels of negative spherical aberration. All three factors are expected to vary between individuals and to be significantly influenced by lifestyle and educational experiences, both of which have been implicated in the generation of myopia.[52,53] Increased outside playtime (with presumed longer viewing distances and smaller pupils) successfully lowered the incidence of myopia onset in a group of Asian children.[54] Restricting myopic defocus to peripheral lens locations, as will happen with a positive spherical aberration multifocal design (e.g., +0.175 µm of C40 over a 5-mm pupil diameter),[16] may fail to slow myopia progression either because pupil sizes are too small to include the required added plus power or because the significant negative spherical aberration of the children's eyes will inevitably reduce or even cancel the positive spherical aberration of a multifocal lens during near viewing.

As with all laboratory studies, this study captures a moment in time. However, by inference, the data provide information about the extended myopic control dosages experienced by young eyes as they are treated throughout the day and over multiple years. By using typical small text displayed on a high-resolution smartphone viewed binocularly, the goal was to capture data that are at some level reasonably representative of a good portion of a child's life. The singular defocus values captured from aberrometry measurements embrace monochromatic aberrations of the eye plus lens combination but, of course, fail to include the spread of defocus contributed by spectral changes in power of the human eye[55] and the effect of soft contact lens decentration on the anterior eye surface.

In conclusion, the data presented in this study reveal a consistent and universal increase in the nominal "stop" signal (more myopic defocus) and a simultaneous reduction in the hypothesized hyperopic defocus "grow" signal[56] in the central retina of children who were being treated with the dual-focus contact lenses. Although studies of infant monkeys have shown that hyperopic defocus outside of the central retina is sufficient to stimulate eye growth,[57] near viewing of small targets such as cell phones or books may only generate hyperopic defocus in and around the central retina, with the noncentral retina being more myopically defocused by virtue of being farther than the near target being viewed.[58]

ARTICLE INFORMATION

Submitted: September 29, 2022

Accepted: April 1, 2023

Funding/Support: None of the authors have reported funding/support.

Conflict of Interest Disclosure: NSL and PSK received financial support from CooperVision. MR is a consultant to CooperVision. PC, BA, and AB are employees of CooperVision. The sponsor participated in study design, analysis, and interpretation. All authors were responsible for the preparation of this article and the decision to submit this article for publication. The investigators at Aston University (NSL, SJ) had full access to the study data; the Indiana University investigators (VR, DM, MJ, MR, PSK) had partial access to the study data and take full responsibility for their presentation in this article. The lead author affirms that the article is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. All investigators take responsibility for the integrity of the data and have critically reviewed the article for important intellectual content.

Author Contributions and Acknowledgments: Conceptualization: VR, NSL, DM, PC, BA, AB, PSK; Data Curation: VR; Formal Analysis: VR, DM, MJ, MR, PC, BA, AB, PSK; Investigation: VR, NSL, SJ, PC, BA, AB, PSK; Methodology: VR, DM, MJ, MR, PC, BA, AB, PSK; Project Administration: NSL, SJ, PC, BA, AB, PSK; Resources: NSL, SJ, AB, PSK; Software: VR, MJ, MR; Supervision: NSL, PC, BA, AB, PSK; Validation: VR; Visualization: VR, DM, AB, PSK; Writing – Original Draft: VR, AB; Writing – Review & Editing: VR, NSL, DM, MJ, MR, PC, BA, AB, PSK.

The authors thank the Clinical Optics Research Lab members for their useful insights on the data analysis.

REFERENCES

1. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016;123:1036–42.

2. Ding BY, Shih YF, Lin LL, et al. Myopia among Schoolchildren in East Asia and Singapore. Surv Ophthalmol 2017;62:677–97.

3. Jung SK, Lee JH, Kakizaki H, et al. Prevalence of Myopia and Its Association with Body Stature and Educational Level in 19-year-old Male Conscripts in Seoul, South Korea. Invest Ophthalmol Vis Sci 2012;53:5579–83.

4. Wildsoet CF, Chia A, Cho P, et al. IMI -- Interventions Myopia Institute: Interventions for Controlling Myopia Onset and Progression Report. Invest Ophthalmol Vis Sci 2019;60:M106–31.

5. Fricke TR, Jong M, Naidoo KS, et al. Global Prevalence of Visual Impairment Associated with Myopic Macular Degeneration and Temporal Trends from 2000 through 2050: Systematic Review, Meta-analysis and Modelling. Br J Ophthalmol 2018;102:855–62.

6. Klaver CC, Wolfs RC, Vingerling JR, et al. Age-specific Prevalence and Causes of Blindness and Visual Impairment in an Older Population: The Rotterdam Study. Arch Ophthalmol 1998;116:653–8.

7. Tang Y, Wang X, Wang J, et al. Prevalence and Causes of Visual Impairment in a Chinese Adult Population: The Taizhou Eye Study. Ophthalmology 2015;122:1480–8.

8. Xiao O, Guo X, Wang D, et al. Distribution and Severity of Myopic Maculopathy among Highly Myopic Eyes. Invest Ophthalmol Vis Sci 2018;59:4880–5.

9. Walline JJ, Walker MK, Mutti DO, et al. Effect of High Add Power, Medium Add Power, or Single-vision Contact Lenses on Myopia Progression in Children: The Blink Randomized Clinical Trial. JAMA 2020;324:571–80.

10. Lam CS, Tang WC, Qi H, et al. Effect of Defocus Incorporated Multiple Segments Spectacle Lens Wear on Visual Function in Myopic Chinese Children. Transl Vis Sci Technol 2020;9:11.

11. Chamberlain P, Peixoto-de-Matos SC, Logan NS, et al. A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control. Optom Vis Sci 2019;96:556–67.

12. Smith EL, 3rd. Optical Treatment Strategies to Slow Myopia Progression: Effects of the Visual Extent of the Optical Treatment Zone. Exp Eye Res 2013;114:77–88.

13. Jaskulski M, Singh NK, Bradley A, et al. Optical and Imaging Properties of a Novel Multi-segment Spectacle Lens Designed to Slow Myopia Progression. Ophthalmic Physiol Opt 2020;40:549–56.

14. Bao J, Yang A, Huang Y, et al. One-year Myopia Control Efficacy of Spectacle Lenses with Aspherical Lenslets. Br J Ophthalmol 2022;106:1171–6.

15. Rappon J, Chung C, Young G, et al. Control of Myopia Using Diffusion Optics Spectacle Lenses: 12-Month Results of a Randomised Controlled, Efficacy and Safety Study (CYPRESS). Br J Ophthalmol 2022;bjophthalmol–2021–321005.

16. Cheng X, Xu J, Chehab K, et al. Soft Contact Lenses with Positive Spherical Aberration for Myopia Control. Optom Vis Sci 2016;93:353–66.

17. Bennsen DA, Sinnott LT, Mutti DO, et al. 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 2012;53:640–9.

18. U.S. Food and Drug Administration (FDA). MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear. Available at: https://www.accessdata.fda.gov/Scripts/Cdrh/Cfdocs/Cfpma/Pma.Cfm?Id=P180035. Accessed September 19, 2022.

19. Arumugam B, Hung LF, To CH, et al. The Effects of Simultaneous Dual Focus Lenses on Refractive Development in Infant Monkeys. Invest Ophthalmol Vis Sci 2014;55:7423–32.

20. Arumugam B, Hung LF, To CH, et al. The Effects of the Relative Strength of Simultaneous Competing Defocus Signals on Emmetropization in Infant Rhesus Monkeys. Invest Ophthalmol Vis Sci 2016;57:3949–60.

21. Singh NK, Meyer D, Jaskulski M, et al. Retinal Defocus in Myopes Wearing Dual-focus Zonal Contact Lenses. Ophthalmic Physiol Opt 2022;42:8–18.

22. Cheng X, Xu J, Brennan NA. Accommodation and Its Role in Myopia Progression and Control with Soft Contact Lenses. Ophthalmic Physiol Opt 2019;39:162–71.

23. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative Lag before and after the Onset of Myopia. Invest Ophthalmol Vis Sci 2006;47:837–46.

24. Nakatsuka C, Hasebe S, Nonaka F, et al. Accommodative Lag under Habitual Seeing Conditions: Comparison between Myopic and Emmetropic Children. Jpn J Ophthalmol 2005;49:189–94.

25. Tarrant J, Severson H, Wildsoet CF. Accommodation in Emmetropic and Myopic Young Adults Wearing Bifocal Soft Contact Lenses. Ophthalmic Physiol Opt 2008;28:62–72.

26. Cheng H, Barnett JK, Vilupuru AS, et al. A Population Study on Changes in Wave Aberrations with Accommodation. J Vis 2004;4:272–80.

27. Lopez-Gil N, Fernandez-Sanchez V. The Change of Spherical Aberration during Accommodation and Its Effect on the Accommodation Response. J Vis 2010;10:12.

28. Plainis S, Ginis HS, Pallikaris A. The Effect of Ocular Aberrations on Steady-state Errors of Accommodative Response. J Vis 2005;5:466–77.

29. Thibos LN, Bradley A, Lopez-Gil N. Modelling the Impact of Spherical Aberration on Accommodation. Ophthalmic Physiol Opt 2013;33:482–96.

30. Altoaimi BH, Almutairi MS, Kollbaum PS, et al. Accommodative Behavior of Young Eyes Wearing Multifocal Contact Lenses. Optom Vis Sci 2018;95:416–27.

31. Howlett MH, McFadden SA. Spectacle Lens Compensation in the Pigmented Guinea Pig. Vision Res 2009;49:219–27.

32. Troilo D, Totonelly K, Harb E. Imposed Anisometropia, Accommodation, and Regulation of Refractive State. Optom Vis Sci 2009;86:E31–9.

33. Smith EL, 3rd, Hung LF. The Role of Optical Defocus in Regulating Refractive Development in Infant Monkeys. Vision Res 1999;39:1415–35.

34. Winawer J, Wallman J. Temporal Constraints on Lens Compensation in Chicks. Vision Res 2002; 42:2651–68.

35. Tse DY, Lam CS, Guggenheim JA, et al. Simultaneous Defocus Integration during Refractive Development. Invest Ophthalmol Vis Sci 2007;48:5352–9.

36. McFadden SA, Tse DY, Bowrey HE, et al. Integration of Defocus by Dual Power Fresnel Lenses Inhibits Myopia in the Mammalian Eye. Invest Ophthalmol Vis Sci 2014;55:908–17.

37. Gifford KL, Schmid KL, Collins JM, et al. Multifocal Contact Lens Design, Not Addition Power, Affects Accommodation Responses in Young Adult Myopes. Ophthalmic Physiol Opt 2021;41:1346–54.

38. Altoaimi BH, Kollbaum P, Meyer D, et al. Experimental Investigation of Accommodation in Eyes Fit with Multifocal Contact Lenses Using a Clinical Auto-refractor. Ophthalmic Physiol Opt 2018;38:152–63.

39. Hammond D, Chamberlain P, Arumugam B, et al. Eye Growth of Children Undergoing Myopia Control Treatment Compared with Emmetropic Eye Growth. Ophthalmologe 2022;119:147–8.

40. Chamberlain P, Bradley A, Arumugam B, et al. Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial. Optom Vis Sci 2022;99:204–12.

41. Kollbaum PS, Bradley A, Thibos LN. Comparing the Optical Properties of Soft Contact Lenses On and Off the Eye. Optom Vis Sci 2013;90:924–36.

42. Kollbaum PS, Jansen ME, Tan J, et al. Vision Performance with a Contact Lens Designed to Slow Myopia Progression. Optom Vis Sci 2013;90:205–14.

43. Kollbaum P, Jansen M, Thibos L, et al. Validation of an Off-eye Contact Lens Shack-Hartmann Wavefront Aberrometer. Optom Vis Sci 2008;85:E817–28.

44. Singh NK, Jaskulski M, Ramasubramanian V, et al. Validation of a Clinical Aberrometer Using Pyramidal Wavefront Sensing. Optom Vis Sci 2019;96:733–44.

45. Applegate RA, Lakshminarayanan V. Parametric Representation of Stiles-Crawford Functions: Normal Variation of Peak Location and Directionality. J Opt Soc Am (A) 1993;10:1611–23.

46. Flitcroft DI, He M, Jonas JB, et al. IMI—Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. Invest Ophthalmol Vis Sci 2019;60:M20–30.

47. Leat SJ. To Prescribe or Not to Prescribe? Guidelines for Spectacle Prescribing in Infants and Children. Clin Exp Optom 2011;94:514–27.

48. Howarth RJ. Sources for a History of the Ternary Diagram. Br J Hist Sci 1996;29:337–56.

49. Bradley A, Nam J, Xu R, et al. Impact of Contact Lens Zone Geometry and Ocular Optics on Bifocal Retinal Image Quality. Ophthalmic Physiol Opt 2014;34: 331–45.

50. Ruiz-Pomeda A, Perez-Sanchez B, Canadas P, et al. Binocular and Accommodative Function in the Controlled Randomized Clinical Trial MiSight® Assessment Study Spain (MASS). Graefes Arch Clin Exp Ophthalmol 2019;257:207–15.

51. Thibos LN, Bradley A, Liu T, et al. Spherical Aberration and the Sign of Defocus. Optom Vis Sci 2013;90: 1284–91.

52. Rose KA, Morgan IG, Ip J, et al. Outdoor Activity Reduces the Prevalence of Myopia in Children. Ophthalmology 2008;115:1279–85.

53. Wu PC, Tsai CL, Hu CH, et al. Effects of Outdoor Activities on Myopia among Rural School Children in Taiwan. Ophthalmic Epidemiol 2010;17:338–42.

54. Wu PC, Tsai CL, Wu HL, et al. Outdoor Activity during Class Recess Reduces Myopia Onset and Progression in School Children. Ophthalmology 2013;120: 1080–5.

55. Ravikumar S, Bradley A, Thibos LN. Chromatic Aberration and Polychromatic Image Quality with Diffractive Multifocal Intraocular Lenses. J Cataract Refract Surg 2014;40:1192–204.

56. Wallman J, Winawer J. Homeostasis of Eye Growth and the Question of Myopia. Neuron 2004;43:447–68.

57. Smith EL, 3rd, Hung LF, Huang J. Relative Peripheral Hyperopic Defocus Alters Central Refractive Development in Infant Monkeys. Vision Res 2009; 49:2386–92.

58. Flitcroft DI. The Complex Interactions of Retinal, Optical and Environmental Factors in Myopia Aetiology. Prog Retin Eye Res 2012;31:622–60.

CHAPTER 8: DISCUSSION AND CONCLUSIONS

For the practice of myopia control to successfully translate into standard clinical practice there must be accompanying evidence that interventions to slow the progression of myopia in children can be safe and effective over the timespan that accelerated eye growth continues. Assessing efficacy of myopia control treatments is complex due to uncontrolled and unknown visual experiences, for example, differing educational demands over time. Concerns about the long-term sustainability of initial myopia control effects and the safety of daily full-time contact lens wear in young children necessitated comprehensive clinical trials to assess both efficacy and safety. This thesis is based upon seven publications derived from the first (and only) six-year clinical study of a myopia control intervention.

This study of a dual-focus soft contact lens aimed to determine whether such a device could be effectively integrated into clinical practice as a myopia control intervention for treating juvenile-onset myopia in a young population. To achieve this, a group of young myopes with no prior contact lens experience were recruited and monitored over a period of six years at regular intervals. The study design provided data to address two key questions: Could soft daily disposable contact lenses be worn safely by the target population over the long term and could this dual focus contact lens slow myopia progression throughout the period in which the condition typically advances in this demographic?

Safety during the study was monitored using standard measures of anterior ocular health, assessed with a slit lamp biomicroscope. This procedure was performed comprehensively every 6 months over the entire 6-year study period. As concluded in Chapter 5, no serious adverse events related to contact lens wear were observed throughout the study. In total, this accounted for 653 subject-years of contact lens wear. Across all examinations within this period, there were only five instances where any graded measure of ocular health was scored as ‘2’ (mild). The annual incidence rate of corneal infiltrative events (CIEs) was 0.61%, equivalent to 61 cases per 10,000 patient-years of wear. This data represents the longest longitudinal assessment of ocular health from contact lens wear in children to date.

A clinical study on myopia control, commonly known as the BLINK study ("Bifocal Lenses in Nearsighted Kids"), (Walline, Walker et al. 2020) also assessed safety outcomes over a three-year period in children of a similar age to those in the MiSight study. As observed in the MiSight study, adverse events were more likely to occur in the first year (Chapters 3 and 5). However, the rate of corneal infiltrative events in the BLINK study was higher, at 197 cases per 10,000 patient-years. This increased rate could be attributed to factors such as the use of reusable lenses with multipurpose care solutions or the difference in lens material (silicone hydrogel vs. hydrogel), both of which have been implicated with a higher incidence of infiltrative events.

A literature review by Bullimore on the safety of soft contact lenses in children reported an incidence rate of 136 cases per 10,000 of CIEs, which included studies involving various modalities and materials. (Bullimore 2017) This rate, along with those from other longitudinal studies, aligns with findings from the CLAY study, (Chalmers, Wagner et al. 2011) which reported a rate of 97 per 10,000 in a similar age group to the BLINK and MiSight studies. The CLAY study also identified an age-related dependency on CIE rates, with higher rates observed in the 13–17 and 18–25 age groups. Other studies have also shown that older teenagers have a higher propensity for CIEs. (Chalmers, Keay et al. 2010, Chalmers, Keay et al. 2012)

It is reasonable to speculate that, aside from age, other modifiable risk factors may contribute to increased CIE rates. Factors such as smoking, rinsing lenses with tap water, overnight wear, and the use of reusable lenses with multipurpose care solutions (often chosen for cost-effectiveness) have been reported to increase the likelihood of CIEs. (Stapleton, Bakkar et al. 2021) For the population in the MiSight study, it is reasonable to speculate that many of these factors are unlikely to be prevalent, given the age and associated parental oversight in this cohort.

The CIE rates reported in studies of younger children compare favorably to those observed in adults. In adults, the rate of CIEs associated with daily silicone hydrogel lens wear is reported at 316 cases per 10,000. (Szczotka-Flynn, Jiang et al. 2014, Bullimore 2017) Implying that fitting daily disposable lenses at a younger age, coupled with proper instruction and compliance, may have a positive impact on reducing CIE incidence. The available evidence indicates that children experience lower CIE rates compared to older age groups, which is reassuring given the full-time wear required by myopia control modalities. The rates observed in the MiSight study are aligned with this general body of evidence that infiltrative events are at acceptable low levels in children wearing daily disposable contact lenses.

Sight-threatening microbial keratitis events are exceedingly rare. The 653 subject-years collected in this trial were insufficient to provide a complete picture of these rates. To address this limitation, the RECSS study (Chapter 5) combined safety data from the MiSight trial with retrospective data from clinical practices that fit large numbers of children matching the MiSight trial's inclusion criteria. The observed infection rate was 7.4 per 10,000, with an upper confidence limit of 29.6 per 10,000. This rate included all contact lens materials and modalities, including the use of multipurpose care solutions— a risk factor not applicable to daily disposable lenses. The observed rate in the RECSS study is higher than the typical 1–2 per 10,000 observed in adults wearing daily disposable lenses. (Stapleton, Keay et al. 2008) Potential explanations of this discrepancy may be the smaller sample size and lower denominator used in the RECSS rate calculation versus established epidemiology studies for rates of microbial keratitis.

Known risk factors for microbial infection (Morgan, Efron et al. 2005, Stapleton, Bakkar et al. 2021) and the observed compliance with contact lens wear in children (chapter 5) provides no clear reason to anticipate an increased infection rate in children using contact lenses for myopia control. The MiSight approval order in the U.S. (https://www.fda.gov/news-events/press-announcements/fda-approves-first-contact-lens-indicated-slow-progression-nearsightedness-children) required a post-market surveillance study to expand on the RECSS findings with a much larger sample, ensuring that the microbial keratitis rate does not exceed 20 per 10,000 (upper confidence limit). This upcoming study will represent the largest prospective collection of contact lens safety data across all age groups and lens types.

The foundation of this dissertation was a traditional parallel group, randomized, controlled, and masked study conducted over three years. The primary objective was to evaluate the potential of a dual focus contact lens to slow myopia progression, referred to as "myopia control efficacy." The two primary endpoints commonly used in clinical trials (Wolffsohn, Kollbaum et al. 2019) to measure this efficacy were changes from baseline of:

1. **Cycloplegic spherical equivalent refraction (SER)** – measured in diopters (D).

2. **Axial elongation (AL)** – measured in millimeters (mm).

The study compared these metrics in the treated group fit with dual focus contact lenses against a demographically matched control group wearing a standard single vision contact lens correction. The effect size was expressed as the absolute difference in the change from baseline of both diopters and millimeters between the groups at each year of the study. These differences between control and treated eyes were also expressed as proportions (%) of the progression observed in the untreated control arm as a way to include the overall progression rates of the measured cohort into a measure of efficacy.

There has been considerable debate regarding the optimal method for expressing myopia control efficacy, which will be explored later in this chapter. (Brennan, Toubouti et al. 2020) The results of this study, after adjusting for potential demographic imbalances across treatment groups, showed a lower progression of myopia in the treatment group by each measure. Specifically, the SER difference after three years was 0.67D, while the AL difference

was 0.28mm, equivalent to a 59% and 52%, respectively, slowing of SER progression and AL growth compared to that observed in the control eyes.

At the time of its completion, Part 1 of this six-year study provided the best evidence of sustained long-term myopia control. More recently, other optical interventions have provided multi-year evidence of myopia control. The previously mentioned BLINK study ("Bifocal Lenses in Nearsighted Kids") evaluated three-year changes in myopia progression using a center distance multifocal contact lenses designed for presbyopia (Biofinity Multifocal). This study recruited and randomized 294 children, with an impressive retention of 292 participants over the full three-year period. The BLINK study included three arms: a control group (wearing Biofinity single-vision lenses by CooperVision Inc.) and two test groups, which used lenses with medium (+1.50D) and high (+2.50D) additional plus power to create myopic defocus.

Similar to the MiSight design, the multifocal lens used in the BLINK study featured a central optic zone for distance vision, with additional power applied in the outer optic zone. However, unlike MiSight, the BLINK lenses did not have alternating power rings, meaning that with larger pupil sizes, the proportion of defocus within the pupil increased (see analysis in Chapter 2). The efficacy results for the medium add power intervention were modest compared to single-vision lenses, so this review will focus on the high add power results. (Walline, Walker et al. 2020)

Myopia progression in the high add treated eyes was 0.23D less than that observed in the control eyes after one year of treatment, which increased to 0.33D by the end of the second year and 0.46D by the end of the third year. For axial length, effect sizes increased from 0.13mm to 0.20mm to 0.23mm at the same time points. Said differently, treatment with the multifocal CL slowed axial growth by 0.13mm in the first year, 0.07mm in the second year and only 0.03mm in the final year suggesting a gradual decline in efficacy over time. (Brennan, Toubouti et al. 2020) The slowing of progression and axial growth observed in the BLINK study were slightly lower than that observed in the MiSight trial (Chapter 3).

Longer-term assessments of spectacle lens and pharmaceutical myopia control interventions have been published recently. (Lam, Tang et al. 2022, Li, Huang et al. 2023, Laughton, Hill et al. 2024) A novel spectacle lens design, incorporating an array of small lenslets approximately 1mm in size, each with +3.50D of defocus, (Gantes-Nuñez, Jaskulski et al. 2023) was initially studied at a single center in Hong Kong over two years. (Lam, Tang et al. 2019) This study randomized 183 subjects into test and control groups, with baseline age and refractive error similar to those in other reported studies. Due to ethical considerations similar to that discussed in Chapter 4, the control group was discontinued after the second year, but the test group was followed for an additional year. (Lam, Tang et al. 2022)

To assess the myopia control effects for the third year, the authors created a demographically matched historical control to estimate untreated progression in the third year. The slowed axial elongation effects were 0.19mm after one year, 0.29mm after two, and 0.37mm after three years of treatment. Once again, these results demonstrate a significant reduction in accrued treatment effect in years 2 and 3.

Another single-center study in China evaluated a different novel lenslet-based spectacle design, randomizing 170 children into a three-arm study for an initial two-year assessment. (Bao, Huang et al. 2022) The inclusion criteria, including age and refractive error, were comparable to those in previous studies. This study featured two test arms with different levels of aspheric lenslets and a single-focus control group. For the purposes of this review, only the results of the "Highly Aspheric Lenslets" (HAL) intervention are considered.

As in the previous study, the control group was discontinued after the initial two years. However, rather than relying on a historical control group, the study recruited an entirely new untreated population for an additional year while switching the original control group to the HAL intervention. (Li, Huang et al. 2023) At the conclusion of the third year, 51 participants remained in the original HAL group. Axial elongation reductions in this group were reported

as follows: 0.24mm after one year, 0.38mm after two, and an additional 0.11mm during the third year—less than half of the progression reduction observed in the first year. (Bao, Yang et al. 2022)

In addition to establishing MiSight as both an effective and safe myopia control treatment, the extensive and detailed data from this trial offered an opportunity to address some of the broad scientific issues current in the field of myopia control, including this observed impact of study duration. The following sections examine the impact of study duration and separately that of age on treatment, evidence of varied treatment effect in individual eyes, the impact of treatment on both normal and pathological eye growth, and finally some insights into practical and ethical inherent in myopia control study designs, and how results from this trial shed light on the core mechanisms driving eye growth dysregulation in myopia.

8.1. Efficacy Over Time and the Impact of Age

Longitudinal studies of myopia control with three-year data, while important for demonstrating continued accrual of treatment gains over time, consistently show diminishing gains with each subsequent year. This trend, observed in other studies of myopia control,(Brennan, Toubouti et al. 2020) and discussed in the MiSight study (Chapter 3), raises an important question:

Do these reduced treatment effects reflect a change in sensitivity to the myopia control signal analogous to reduced efficacy of some drug therapies (e.g. cancer drugs), (Komarova 2006) or are these changes a reflection of the changing pathology cycle unrelated to treatment (e.g. if there is no myopia progression, myopia control treatment cannot slow this progression)?

An examination of adjusted axial elongation in the treatment group from the BLINK study data reveals a growth rate of 0.16mm in the first year, followed by 0.14mm in the second year and 0.12mm in the third year—representing an annual reduction in growth between 12% and 14% as the treatment group ages. On its own, this pattern does not suggest that the treatment effectiveness is short-lived. Similarly, the test group in the DIMS study exhibited a consistent progression of approximately 0.10mm per year across all three years. In contrast, the treated HAL group showed axial elongation of 0.12mm, 0.20mm, and 0.17mm in years one, two, and three, respectively. Notably, the second-year increase in this group may have been influenced by COVID-19-related lockdowns, which could have had an unknown impact on eye growth. (Bao, Huang et al. 2022)

Well-established growth models suggest that untreated axial elongation naturally slows by an average of 15% per year with age. (Brennan, Shamp et al. 2024) This pattern has been observed across different ethnicities (Asian and non-Asian), age groups, and levels of myopia. A 15% reduction in progression will result in a greater absolute year on year slowing in a fast-progressing Asian population relative to a slower progressing non-Asian population, as is evidenced within this meta-analysis. Thus, when assessing myopia control efficacy by comparing treated growth to that of control eyes which are themselves slowing by 15% complicates the assessment of sustained efficacy. For example, this pattern of 15% slowing per year will result in greater absolute year on year slowing in a faster growing group of untreated eyes and thus smaller year on year differences between them and the parallel treated cohort progressing more slowly. If this general rule applies, it raises important questions about the continued treatment efficacy of myopia control interventions: Could decreased absolute slowing in axial elongation measured as the difference in growth of treated and control eyes over time simply reflect this mathematical trend in the untreated control eyes? Or, more concerningly, does the data suggest that the treatment is not producing further reductions in eye growth as subjects age?

Separating a true change in efficacy from a change in the pathology itself is complicated because of the always present covariate of age. For every subsequent year of treatment, the child is always a year older. The MiSight trial had annual growth rates from treated and control eyes spanning the age range from 8 to 17. Subjects were pooled based on their age at the

start of each study year, regardless of the number of years they had participated in the trial (Figure 11). (Arumugam, Bradley et al. 2021)

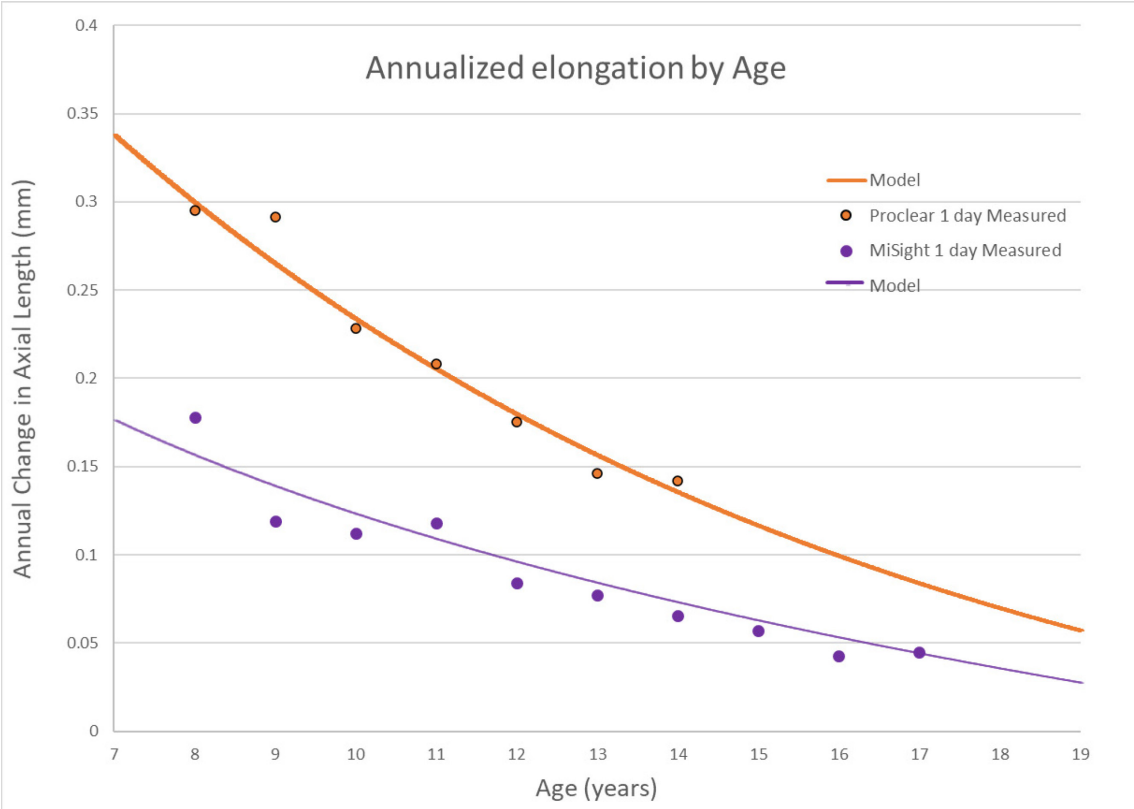


Figure 11: Annualized changes in axial length (ALmm/yr.) is plotted as a function of subject age at the start of the year over which growth was measured for control (orange symbols) and treatment (purple symbols) groups. Univariate models for Estimated Annualized Elongation (EAnE) were created for the untreated population (P1d, orange line) and treated populations (M1d, purple line) respectively.

	Age at Start of Year											Cumulative Axial Elongation
	8	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Control	0.30	0.26	0.23	0.21	0.18	0.16	0.14	0.12	0.10	0.08	0.07	**1.84 mm**
Treatment	0.16	0.14	0.12	0.11	0.10	0.08	0.07	0.06	0.05	0.04	0.04	**0.97 mm**
												Cumulative Difference in Growth Rates
Difference in Growth Rates (mm)	0.14	0.13	0.11	0.10	0.08	0.07	0.06	0.05	0.05	0.04	0.03	**0.87 mm**
Difference as %	48	48	47	47	47	46	46	46	47	48	49	**47%**

Table 2: Annualized changes in axial length (ALmm/yr.) is tabulated as a function of subject age at the start of the year over which growth was measured for control and treatment groups.

Annual growth rates for both groups, as shown in Table 2, slowed by approximately 15% (+/- 5%) per year. This suggests that eye growth decreased with age at a similar rate in both treated and untreated populations. While the absolute treatment effect diminishes over time, it remains stable as a percentage of untreated growth.

This pattern aligns with findings from the traditional cohort analysis (Chapter 6), which show a yearly decline in absolute treatment effects but an approximately consistent percentage reduction in eye growth (Table 1, Chamberlain et al, 2023). A similar trend is observed in the Stellest HAL 5-year treatment data (Figure 2 and in (LI, Huang et al. 2024). In year 1, the treatment effect was 0.22 mm; however, instead of accumulating to 1.1 mm over five years (5 × 0.22 mm), it resulted in a total reduction of 0.73 mm. Despite this decline in absolute terms, the treatment effect remained relatively stable as a percentage of control growth, decreasing only slightly from 58% after one year to 52% after five years. A similar modest decline was observed in the cohort data in the MiSight study with percentage efficacy decline from 68% in year 1 to 52% after six years.

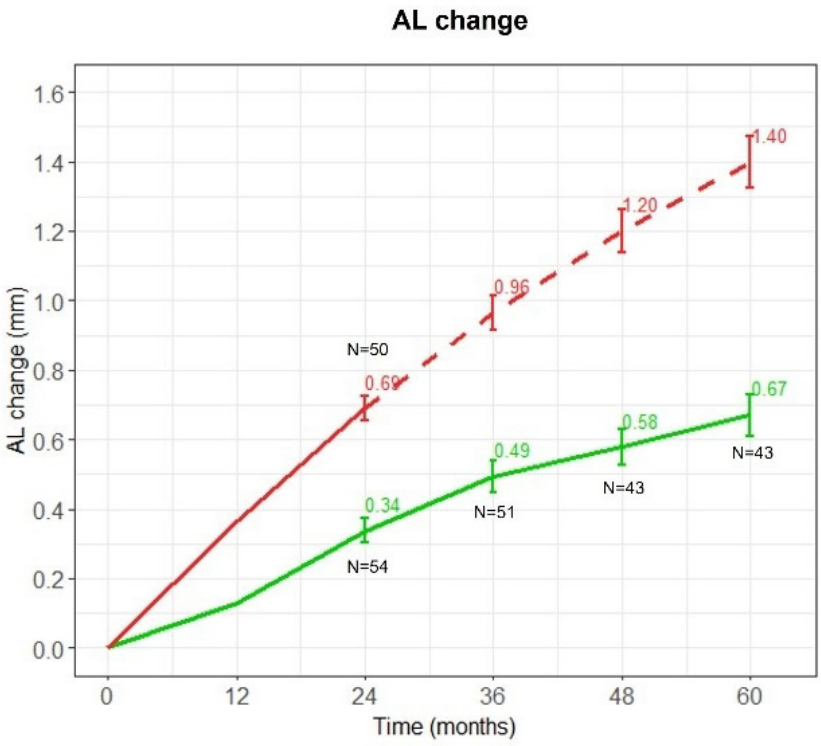


Figure 12: Axial elongation in treated (HAL, Green) and untreated (Red), presented in (LI, Huang et al. 2024)

The consistent treatment effect, when expressed as a proportion of untreated growth, is likely due to the natural progression of eye growth with age and underlying pathological cycles. This finding suggests that quantifying treatment effects as a proportion or percentage of the study control eye growths may provide a strategy to compare treatment efficacy across different durations, ages, and ethnicities.

8.2. Treatment Heterogeneity

Clinical trials with parallel treatment and control groups assess efficacy by comparing the mean outcomes of both groups, producing a single treatment effect value. This value is then used to evaluate the overall effectiveness of the treatment. However, when efficacy is expressed in absolute terms, it can present a concerning scenario for rapidly progressing eyes. For example, an average reduction of 0.25D per year would indicate a highly effective treatment for eyes that would have progressed by 0.25D/yr if left untreated, but for an eye progressing at 1D per year or more, this would represent a relatively poor outcome.

Moreover, data from traditional randomized controlled trials (RCTs) provide no insight into the treatment effects on individual eyes. The RCT design used in the first three years of this trial only measures overall group differences, making it impossible to determine how much an individual eye's growth or progression has changed due to treatment. The unique design of Part 2 of the MiSight study afforded an opportunity to explore individual responses to treatment by comparing growth of the control group during years 1-3 with the growth of the same subjects in treatment during the subsequent 3 years. This analysis detailed in chapter 4 revealed a subset of eyes where progression of eye growth did not slow when entering treatment and were classed as 'non-responders'. Figure 4 from the published manuscript in chapter 6 also reveals the treatment response of eyes that were slower or faster progressing prior to treatment. Eyes that progressed faster prior to treatment (years 1-3) (x axis) exhibited the greatest amount of slowing in treatment during years 4-6 (separation of data point from the Y=X line).

The observation that faster progressing eyes receive the greatest absolute treatment effect can be challenged as “regression to the mean” in that in a noise dominated data set higher values at time 1, will be more likely to be closer to the mean and hence lower at the second measurement. (Atkinson and Batterham 2015, Mutti, Sinnott et al. 2022) Such a regressive trend is expected if growth from year to year was dominated by individual variability in growth rates unrelated to treatment and if there was little or no treatment effect. A subsequent analysis based on the data from the manuscript in chapter 4 pooled the faster and slower quartiles of control eyes based upon pre-treatment growth over 3 years and revealed groups with consistently faster and slower year-on-year average growth and progression for all 6 years contrary to a regression to the mean expectation (Table **3**). (Chamberlain, Arumugam et al. 2022) Finally, evidence that faster growing eyes slow in subsequent (treated) years cannot be used as evidence of regression to the mean without a concurrent observation that slower growing eyes subsequently accelerate their growth (toward the mean) during the same treatment years. Contrary to this latter expectation, treated growth of the slower eyes in Table **3** remained slower than each year prior to treatment and slower than all three other quartiles when averaged across the three years of treatment. The observation (Figure 4 chapter 4, and Table 3) that faster progressing and younger eyes experience the greatest change in growth once treatment began is confirmation that not all eyes receive the same treatment effect, and the observed treatment effects in mm approximately scale with the magnitude of the accelerated growth prior to treatment.

		Pre-treatment			Myopia Control Treatment		
	Year	1	2	3	4	5	6
Axial Growth (mm/yr.)	Q1	0.07	0.09	0.06	0.02	-0.01	0.05
	Q2	0.19	0.21	0.13	0.00	0.05	0.04
	Q3	0.32	0.25	0.18	0.03	0.06	0.06
	Q4	0.42	0.34	0.29	0.07	0.03	0.09
Myopia Progression (D/yr.)	Q1	-0.25	-0.23	-0.10	-0.04	0.02	-0.02
	Q2	-0.55	-0.32	-0.20	-0.03	-0.15	-0.02
	Q3	-0.61	-0.40	-0.35	0.00	-0.15	-0.08
	Q4	-1.03	-0.49	-0.51	-0.11	-0.23	0.03

Table 3: Annual axial growth and myopia progression of the majority eyes that slowed progression during treatment grouped by quartiles (Q1-Q4). Quartiles were defined using the accumulated axial growths observed during years 1-3.

A small but unique group of 9 eyes failed to show any evidence of slowed growth once treatment began. Evidence of the existence of this subgroup relied on convergent, well-studied statistical learning, clustering, and regression approaches (Chapter 4). The underlying latent structure in the axial growth data revealed by these algorithms is consistent with a heterogeneous treatment effect where most eyes respond to myopia control treatment (“responders”) while a minority do not (“non-responders”). However, it is possible that failure to observe a treatment effect in individual cases may reflect inherent within-subject variability in the measured outcome variable masquerading as treatment heterogeneity. (Atkinson and Batterham 2015) In studies lacking pre-treatment data, utilizing the absolute growth and myopia progression during treatment may not reflect treatment heterogeneity because as revealed in Chapter 4 some eyes grow and progress faster than others both with and without treatment. (Brennan, Toubouti et al. 2020, Charman and Radhakrishnan 2021) In the present

analysis, the term “non-responder” is applied only to those eyes that exhibited the same significant growth prior to and during treatment, which may be a conservative estimate given the established 15% slowing each year, but given the unknown applicability to individuals of that analysis was considered an appropriate categorization (Chapter 4, Figure 4). It can also be seen in Chapter 4 that there are treated eyes that grew at rates as fast as some of the “non-responder” eyes, but they were included in the majority responder group because their growth during treatment slowed significantly from their pre-treatment rates. Ironically, if response to treatment was assessed by monitoring the absolute growth rates during treatment, the faster progressing eyes in the present study would be considered to have the least treatment effect in that they grew faster during treatment than other treated eyes ($slope\ \hat{\beta} = 0.29$). However, these eyes experienced the greatest slowing once treatment had begun. Therefore, by an absolute growth criterion, these eyes would be considered least responsive to treatment, but based upon change in growth rates, they are the most responsive to treatment. Without tracking prior growth rates, this distinction would be lost.

Although within-individual comparisons of pre-treatment and during treatment effects control for both measured and unmeasured time-invariant variables (e.g. gender and race), the approach of using changes in progression or growth once treatment begins remains susceptible to time-varying factors or individual changes in the study subjects associated with growth and progression but unrelated to treatment. As emphasized by other publications, (Senn 2004, Kent, Steyerberg et al. 2018, Atkinson, Williamson et al. 2019) changes in response of individuals may not provide unambiguous evidence of treatment success (or failure) because of variations over time unrelated to the treatment effect. Senn suggests that a repeat cross-over design in which treatment is repeatedly alternated with a control on some random schedule is the most rigorous approach for assessing treatment effects in individual cases, but even this approach comes with limitations and is likely to be impractical for assessing myopia control efficacy since each phase of this design may have to last one or more years. (Guyatt, Sackett et al. 1988)

Comparison of single measures of pre-treatment and during treatment outcome measures are vulnerable to inherent variability in these measures making assessment of treatment efficacy from such data tenuous at best. (Atkinson and Batterham 2015) The current investigation had three repeat measures of individual eye axial growth and myopia progression prior to and then during treatment offering an opportunity to identify consistent changes accompanying treatment.

The data from this study suggest that limiting investigations to a single measure of efficacy unnecessarily restricts the ability to fully understand the long-term performance of an intervention. While debates over appropriate efficacy measures continue, the evidence reviewed in this chapter tells a consistent story: successful optical interventions for myopia control demonstrate cumulative effects over multiple years and the magnitude of these effects scale with the severity of progressions and axial growth that would have happened if left untreated. Treatment works best for those most in need of slowed growth.

8.3. Normal Eye Growth and Myopia Control

The data presented in Chapter 6 (Chamberlain, Jara et al. 2021) showed that the mean axial elongation of the treated population closely matched the mean growth of an age-matched population of non-myopic subjects. This finding was later expanded in Chapter 6, (Chamberlain, Hammond et al. 2024) demonstrating that non-myopic axial growth rates remained similar to those observed in the treated population across all six years of the study, including in the subgroup that began treatment at an older age (Figure 1, (Chamberlain, Hammond et al. 2024)). However, while treated axial growth rates resemble those of emmetropic eyes, some degree of myopia progression still occurred. (Chamberlain, Peixoto-de-Matos et al. 2019, Chamberlain, Bradley et al. 2022) The presence of myopia progression in eyes growing at emmetropic rates suggests an inherent inability of already myopic eyes to fully compensate for normal (emmetropic) rates of axial elongation. Restated, unlike

emmetropic eyes that can increase their axial length during childhood and teenage years without developing myopia, the same level of axial growth in already myopic eyes will be reflected with increase in refractive error.

Since both emmetropic and myopic eyes both grow throughout childhood and adolescence (Mutti, Rozema), (Mutti, Sinnott et al. 2023, Rozema, Dankert et al. 2023) growth that does not generate myopia has been labelled normal or "physiological eye growth," whereas eye growth that creates myopia is considered "pathological eye growth". More recently, these two “types” of eye growth have been characterized as “compensated” (axial growth is accompanied by optical changes that create a matched extension of the optical length of the eye) and “uncompensated” (extra axial growth that is not accompanied by a matching increase in the optical length of the eye). (Mutti, Sinnott et al. 2023) The 6-year axial growth data and emmetropic comparisons shown in Chapter 6 highlight that normal eye growth occurs over a similar age span as the progression of myopia. (Comet Group 2013, Qin, Peng et al. 2022) The following section examines the relationship between axial growth and myopia progression in both untreated and treated eyes to explore the presence of compensated and uncompensated eye growth.

The close relationship between extra eye growth and myopia has been long established, (Carroll 1982, Scott and Grosvenor 1993) and Gullstrand’s "exact" and "simplified" schematic eyes reveal that if axial length alone changed (zero compensatory changes in the eyes optics to lengthen the focal length of the eye), then - 2.57D (exact) and -2.67 (simplified) diopters of myopia would accompany each mm of axial growth for an eye length similar to the population enrolled into the MiSight trial. The gain (D/mm) will be greater for smaller (younger) eyes exceeding 4D/mm at 1 year of age. (Mutti, Sinnott et al. 2018) Although some early data reported slopes >-2.5D/mm, (Carroll 1982) Mutti et al. (2023) observed less myopia progression per mm of axial growth than predicted from a pure axial elongation model with slopes closer to -2D/mm, Table 2, (Mutti, Sinnott et al. 2023). That slope value, less than that predicted by solely axial growth of the posterior eye indicates that some compensatory optical changes are also happening in progressing myopes.

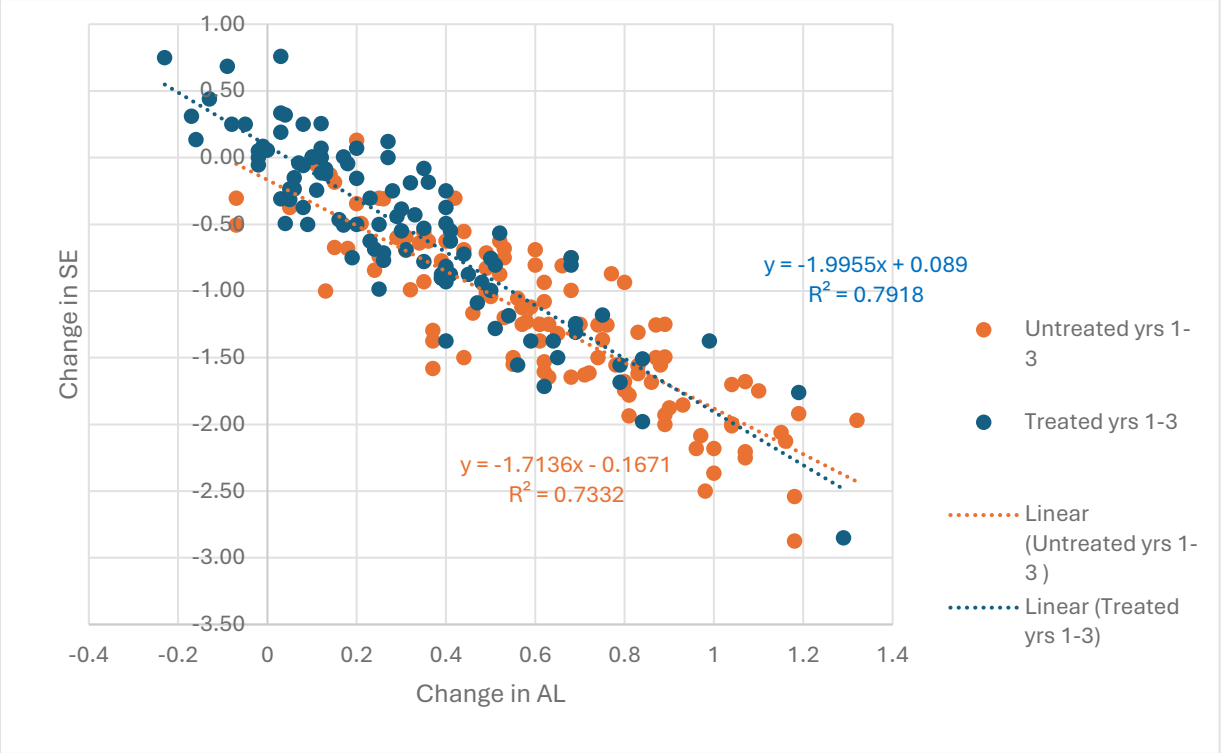


Figure 13: Scatterplot of change of change in SER (D) per millimeter of axial length (AL) change (mm) for untreated (orange) and treated (blue) populations in Part 1 of the MiSight study

Figure 13 illustrates an expected high correlation for changes in AL and SER for untreated (R2 = 0.73) and treated (R2 = 0.79) eyes. During Part 1 (years 1-3) the best fit linear regression slope for the treated eyes was close to 2D/mm, with a similar slope observed for the untreated population. The slopes of approximately 2D of progression per mm of axial length change, are similar to that observed in a like aged myopic population by Mutti et al. (Mutti, Sinnott et al. 2023) The comparable slopes observed in both treated and untreated populations suggest that the relationship between myopia progression and axial elongation in myopic eyes remains unaffected by myopia control treatments that slow axial growth by >50%. If the MiSight population had achieved non-myopic growth solely by eliminating pathological eye growth, we would expect a different growth relationship compared to the untreated population, one where eye growth only slightly greater than that observed in age matched emmetropic eyes resulted in minimal refractive error progression. Conversely, if the treatment had only interrupted physiological eye growth, the treated group would have shown a progression rate closer to 2.5D per mm, as expected in an eye without compensatory changes in the anterior eye optical components. The unchanged slopes of slightly less than 2D/mm during treatment provides no clear evidence that MiSight treatment affects only one of these two possible distinct mechanisms (physiological vs. pathological) governing eye growth. This finding has broader implications for future myopia control efforts: unless a therapy can selectively target pathological eye growth while preserving physiological growth, without inducing refractive error changes, achieving a complete cessation of myopia progression (100% slowing) may not be a feasible outcome. Additionally, achieving 100% slowing by imparting zero growth over multiple years in a population whose age matches that of emmetropic children that still display physiological eye growth, also seems an implausible scenario.

8.4. Exploring Mechanisms of Myopia Control for Current Optical Interventions

Myopia control effects observed in this study were achieved with defocus created by the add power included in the annular treatment zones of MiSight contact lenses. Similarly, defocus generated with small lenslets with positive add power in spectacle lenses has also been shown to slow myopia progression. (Lam, Tang et al. 2019, Bao, Yang et al. 2022) Since the commercial launch of these myopia control spectacle products, optical engineers have characterized the optics of these lenslets with high precision. (Gantes-Nuñez, Jaskulski et al. 2023) This characterization highlights a significant difference between the defocus designs of spectacle lenses and the MiSight lens. Specifically, the imaging properties of the lenslets in spectacle designs indicate that they do not combine to create a common on-axis image, which is created by the combined annular treatment rings of MiSight. Each of the spectacle lens lenslets have foci displaced from the base optic axis and as such are referred to as having “non-coaxial” optics. As Gantes Nunez et al. observed, adding these lenslets creates a significant diffraction blur and lowered image contrast. Theoretically, these optics will also eliminate any presence of peripheral hyperopia, in this case, simply due to the lack of imaging properties in the spectacle periphery. This unique feature may indicate an interesting nuance to proposed mechanisms of action theories. Could myopia control effects result from the elimination of a hyperopic ‘grow’ signal rather than the introduction of a myopic defocus ‘stop’ signal?

Beyond the extensive evidence from animal and human trials demonstrating the role of defocus in myopia control, another hypothesis suggests that reducing retinal image contrast across the retina may also slow myopia progression. (Neitz and Neitz 2024) This intervention has been introduced into a myopia control spectacle lens commercially known as the DOT lens. The theory stems from studies on individuals with Bornholm disease, a genetic disorder that results in extreme myopia. Research by Neitz suggests that in these patients, some of either the L (long-wavelength) or M (medium-wavelength) cones lack photopigment, disrupting normal photon capture. This results in a constant differential photon absorption and thus neural signal from adjacent cones, causing the midget bipolar cells to perceive persistently high contrast images. The hypothesis proposes that this excessive contrast signaling drives extreme myopia progression. Thus, the DOT lens aims to reduce retinal image contrast by incorporating scattering elements, thereby decreasing differential contrast signaling in the midget bipolar cells. A single four-year study has reported promising results supporting this approach. (Laughton, Hill et al. 2024)

Another proposed mechanism explains how defocus-inducing optics may suppress eye growth signals. The peripheral optics of the eye are naturally aberrated, limiting the retina’s ability to detect fine image-plane changes or contrast variations. Asymmetric aberrations increase with eccentricity, resulting in retinal image structures that differ significantly in the presence of either myopic or hyperopic defocus. These aberrations, therefore provide a possible signed cue for eye growth, and may play a key role in regulating eye growth. (Ji, Yoo et al. 2018) Optical simulations suggest that dual-focus lenses, such as MiSight, reduce this directional blur anisotropy, which may weaken any peripheral signed signal for continued axial elongation, effectively slowing eye growth. (Ji, Yoo et al. 2018)

Does this heterogeneity of successful interventions provide insight into the mechanisms of myopia control? More specifically, do all optical interventions ultimately work by reducing retinal contrast? This question remains challenging to answer definitively.

As outlined, all currently proven optical interventions for myopia control—including myopic defocus, contrast reduction, and blur anisotropy reduction—occur simultaneously in these treatments. This makes it difficult to determine whether contrast reduction alone is responsible for slowing progression or if multiple independent mechanisms contribute to myopia development and its control. Further research is needed to disentangle these

overlapping effects and clarify whether contrast reduction is the primary mechanism or just one of several factors influencing eye growth regulation.

8.5. Ethics and the Future of Myopia Control Studies

Part 2 of this study demonstrated continued myopia control efficacy through the validation and use of a predictive growth model for untreated myopia progression—a so-called "virtual control group". (Brennan, Shamp et al. 2024) The ethical reasoning for eliminating the parallel control group in the MiSight study was discussed in detail in Chapters 4 and 6. Similar practical (recruitment and retention) and ethical concerns have motivated other studies to employ virtual control data when seeking to quantify long-term efficacy. (Bullimore and Brennan 2023, Chen, Liu et al. 2023, LI, Huang et al. 2024, Zhang, Zhang et al. 2024)

As myopia control interventions gain regulatory approval in various countries, ethical and practical challenges related to control group recruitment and retention are becoming more pronounced. Highly educated, higher-income parents—more aware of myopia control options—may increasingly be reluctant to enroll their children in trials with a possible 50% chance of receiving placebo treatments over multiple years. Given the established relationship between socioeconomic status and myopia prevalence, this reality could also bias future trial populations that wish to employ untreated control groups.

Alternative study designs are emerging to address these challenges. (Bullimore, Brennan et al. 2023) For instance, if a new intervention aims to supersede or match effectivity of an existing treatment, direct comparisons with statistical planning for non-inferiority or superiority can be employed, ensuring that all trial participants receive a treatment. The maturation of myopia research, combined with the growing availability of long-term progression data and the potential of electronic health records, offers opportunities for significant advancements in this field. Integrating these data sources with machine learning and big data methodologies could yield transformative insights, building on the foundational work discussed in Chapter 6.

8.6. Post-Treatment Growth and Rebound Effects

Following multi-year accruals of slowed myopia progression, it is imperative that evidence is provided to the clinical community that these treatment gains will be retained once treatment is ceased. The completion of treatment in the 6-year MiSight trial offers an opportunity to investigate retention of treatment gains after treatment cessation at ages, and following a treatment duration, that would expect to be observed in clinical practice. (Bullimore and Brennan 2025) Based on a review of the current evidence base, Bullimore concluded that soft lens interventions resulted in eye growth following treatment cessation that would not be classed as ‘rebound’.

The term rebound has been applied to any acceleration of growth or progression after treatment cessation, (Chiu, Tsai et al. 2023) which fails to capture the crucial distinction of age-normal growth of untreated eyes versus greater than age-normal growth. (Bullimore and Brennan 2025) Age-normal growth after treatment cessation returns an eye to growth levels that would have been experienced without treatment and, therefore, the smaller and less myopic eye created by prior treatment will continue to be smaller and less myopic than if the patient had not been treated. However, if post-treatment growth and progression accelerates to greater than expected for untreated myopic eyes of a given age, the faster-than-expected accelerated growth will start to eliminate prior treatment gains. (Tong, Huang et al. 2009, Chia, Lu et al. 2016, Cho and Cheung 2017, Xiong, Zhu et al. 2022) Indiscriminate use of “rebound” terminology to describe any increased eye growth after treatment cessation fails to recognize the different clinical implications of these two types of post-treatment growth. (Sánchez-Tena, Ballesteros-Sánchez et al. 2024) Upon treatment cessation, do eyes return to age-normal or greater than age-normal growth and progression? The conclusion of the 6-year MiSight trial offers an ideal opportunity to assess this in the future.

8.7. Future Direction

Despite maintaining a myopia control efficacy above 50% over six years, with growth resembling that of non-myopic populations, opportunities remain to enhance efficacy. As discussed in Chapters 4 and 6, variability in individual responses, including non-responders, suggests a need for strategies to provide effective treatment to all progressing myopes. Addressing non-responders or achieving more consistent outcomes across the treated population could provide practitioners with more effective management tools.

Currently, there is no established dose-response relationship for optical interventions, nor a method to predict or measure the optimal dose (see chapter 7) for each child undergoing treatment. In pharmacological interventions, such as atropine, evidence shows that higher concentrations lead to greater myopia control. (Huang, Wen et al. 2016, Yam, Jiang et al. 2018) In animal models, increasing either the diopters (Tse, Lam et al. 2007) or regional coverage area of myopic defocus (Tse, Lam et al. 2007, Liu and Wildsoet 2011, Liu and Wildsoet 2012, Arumugam, Hung et al. 2016) have shown dose-response effects. Studies using higher add powers or increased contrast attenuation in humans have yielded inconclusive results. (Walline, Walker et al. 2020, Rappon, Chung et al. 2023) Long-term studies in children are inherently challenging, but a systematic investigation of dual-focus lens designs—such as increasing diopters of myopic defocus or expanding pupil coverage could provide identify designs with increased efficacy.

Increasing the proportion of the pupil containing treatment optics may reduce retinal contrast as well as increase the amount of defocused light in the image. However, such designs must ensure acceptable vision quality, comfort and allow consistent sustained wearability, and normal accommodative function. Limited evidence from orthokeratology suggests that increased area of myopic regions of the pupil correlates with slower eye growth, but this finding remains underexplored in randomized controlled trials. (Wang, Yang et al. 2018, Chen, Guo et al. 2024)

If optimizing optical interventions alone does not achieve sufficient efficacy, combining them with pharmacological treatments like atropine could provide additional benefits. While low-dose atropine (0.01%) combined with optical interventions has not shown additive effects (Jones, Mutti et al. 2022) this may reflect the limited efficacy of such a low concentration. (Jawaid, Saunders et al. 2024) A modest dose response was achieved when combining 0.01% concentration of atropine with orthokeratology. (Tan, Ng et al. 2023) It is not clear whether supplemental efficacy of adding atropine works because atropine and optical myopia control interventions work by the same or different mechanisms. Also, the impact of atropine may partly result from pupil dilation enhancing myopic defocus.

Combination drug-device products would also face stricter regulatory requirements. Atropine is typically administered as a single drop before bedtime to minimize side effects like accommodation disruption and pupil dilation. (Chia, Chua et al. 2012) Such a dosing regimen would be challenging to implement with a combination product, where release of an agent from a device such as a contact lens will follow a zero order release profile, (Yoshida, Sakai et al. 1991) which again would require added evidence to prove retention of initially proven synergistic effects achieved via a traditional dosing regimen. Could a combination device reduce cohort eye growth under treatment to near-zero levels? Alternatively, would it selectively slow the progression of faster-progressing patients or non-responders to existing treatments, thereby reducing the standard deviation of eye growth rates in the treated population?. (Brennan, Toubouti et al. 2020)

8.8. Conclusion

In summary, this work has shown that an intervention based on the principle of delivering myopic defocus (with accompanying reduction in contrast) to the retina can sustain slowed eye growth for multiple years. This slowed eye growth was also shown to be evident across the majority of eyes who were treated for the 3 years of Part 2 and that slowing was

proportional to the rate of progression prior to treatment. Therefore, when a myopia control response is observed in eyes fit with the MiSight lens, fast progressing eyes will experience the greatest absolute reduction in eye growth. The decline in absolute treatment effects during each successive year of the 6-year trial was consistent with an overall slowing of myopia progression as the children aged, and approximately maintained a stable percentage treatment effect for 6 years. For instance, the slowing of axial elongation for the population was observed to be 52% after 3 years (Chapter 3) and remained 52% after six years (Chapter 6).

Issues surrounding the best approach to slow myopia progression, the most appropriate methods to assess efficacy, and what constitutes an optimum myopia control intervention and indeed the true mechanism of action for these optical devices remain active areas of research today. This PhD thesis is an example of successful multi-year effectiveness on what amounts to the first generation of optical devices for the slowing of myopia progression. The increasing range of effective myopia control interventions offer the eye care practitioners and patients to select myopia control interventions most suited to their age and lifestyle needs. Most significantly, the results in this thesis and other studies make it possible to prevent children from developing high myopia and its accompanying high risk of untreatable sight loss later in life.

References

Abrahamsson, M. and J. Sjöstrand (1996). "Natural history of infantile anisometropia." British Journal of Ophthalmology 80(10): 860-863.

Adler, D. and M. Millodot (2006). "The possible effect of undercorrection on myopic progression in children." Clinical and Experimental Optometry 89(5): 315-321.

Aller, T. A., M. Liu and C. F. Wildsoet (2016). "Myopia Control with Bifocal Contact Lenses: A Randomized Clinical Trial." Optometry and Vision Science 93(4): 344-352.

Altoaimi, B. H., P. Kollbaum, D. Meyer and A. Bradley (2018). "Experimental investigation of accommodation in eyes fit with multifocal contact lenses using a clinical auto-refractor." Ophthalmic and Physiological Optics 38(2): 152-163.

Alvord, L., J. Court, T. Davis, C. F. Morgan, K. Schindhelm, J. Vogt and L. Winterton (1998). "Oxygen permeability of a new type of high Dk soft contact lens material." Optometry and Vision Science 75(1): 30-36.

Anderson, H. A., A. Glasser, R. E. Manny and K. K. Stuebing (2010). "Age-related changes in accommodative dynamics from preschool to adulthood." Investigative Ophthalmology & Visual Science 51(1): 614-622.

Anstice, N. S. and J. R. Phillips (2011). "Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children." Ophthalmology 118(6): 1152-1161.

Arumugam, B., A. Bradley, D. Hammond and P. Chamberlain (2021). "Modelling Age Effects of Myopia Progression for the MiSight 1 day Clinical Trial." Investigative Ophthalmology & Visual Science 62(8): 2333-2333.

Arumugam, B., A. Bradley, D. Hammond, M. Rickert, J. Jiang, X. Yang, R. Wei and P. Chamberlain (2024). Efficacy of MiSight 1 Day Dual Focus Lenses in Controlling Myopia Progression in Chinese Children. American Academy of Optometry. Indianapolis, USA.

Arumugam, B., L. F. Hung, C. H. To, B. Holden and E. L. Smith (2014). "The effects of simultaneous dual focus lenses on refractive development in infant monkeys." Investigative Ophthalmology and Visual Science 55(11): 7423-7432.

Arumugam, B., L. F. Hung, C. H. To, P. Sankaridurg and E. L. Smith, III (2016). "The Effects of the Relative Strength of Simultaneous Competing Defocus Signals on Emmetropization in Infant Rhesus Monkeys." Investigative Ophthalmology & Visual Science 57(10): 3949-3960.

Atchison, D. A., S. Blazaki, M. Suheimat, S. Plainis and W. N. Charman (2016). "Do small-aperture presbyopic corrections influence the visual field?" Ophthalmic and Physiological Optics 36(1): 51-59.

Atchison, D. A. and R. Rosén (2016). "The Possible Role of Peripheral Refraction in Development of Myopia." Optometry and Vision Science 93(9): 1042-1044.

Atkinson, G. and A. M. Batterham (2015). "True and false interindividual differences in the physiological response to an intervention." Experimental Physiology 100(6): 577-588.

Atkinson, G., P. Williamson and A. M. Batterham (2019). "Issues in the determination of 'responders' and 'non-responders' in physiological research." Experimental Physiology 104(8): 1215-1225.

Bao, J., Y. Huang, X. Li, A. Yang, F. Zhou, J. Wu, C. Wang, Y. Li, E. W. Lim, D. P. Spiegel, B. Drobe and H. Chen (2022). "Spectacle Lenses With Aspherical Lenslets for Myopia Control vs Single-Vision Spectacle Lenses." JAMA Ophthalmology 140(5): 472-478.

Bao, J., A. Yang, Y. Huang, X. Li, Y. Pan, C. Ding, E. W. Lim, J. Zheng, D. P. Spiegel, B. Drobe, F. Lu and H. Chen (2022). "One-year myopia control efficacy of spectacle lenses with aspherical lenslets." British Journal of Ophthalmology 106(8): 1171-1176.

Berntsen, D. A. and C. E. Kramer (2013). "Peripheral Defocus with Spherical and Multifocal Soft Contact Lenses." Optometry and Vision Science 90(11): 1215-1224.

Berntsen, D. A., L. T. Sinnott, D. O. Mutti and K. Zadnik (2012). "A Randomized Trial Using Progressive Addition Lenses to Evaluate Theories of Myopia Progression in Children with a High Lag of Accommodation." Investigative Ophthalmology & Visual Science 53(2): 640-649.

Berntsen, D. A., A. Tićak, D. J. Orr, A. G. Giannoni, L. T. Sinnott, D. O. Mutti, L. A. Jones-Jordan, J. J. Walline, B. L. i. N. K. S. Group, D. F. Everett, J. Le, K. J. Shaw, J. H. Jones, B. E. Dougherty, M. A. Boatman, M. L. Robich, P. S. Wessel, G. L. Mitchell, L. Cardenas, K. L. Schulle, D. V. Retnasothie, M. K. Walker, M. A. Chandler, M. T. Nguyen, L. A. Hair, A. N. Nti, J. R. Assaad, E. S. Tomiyama, J. A. Myers, A. D. Nixon, K. M. Bickle, G. E. Pierce, K. S. Reuter, D. J. Gardner, M. Kowalski, A. Morrison, R. L. Fenton, J. T. Holbrook, J. Gwiazda, T. B. Edrington, J. M. Jackson and C. E. Joslin (2025). "Axial Growth and Myopia Progression After Discontinuing Soft Multifocal Contact Lens Wear." JAMA Ophthalmology 143(2): 155-162.

Bradley, A., J. Nam, R. Xu, L. Harman and L. Thibos (2014). "Impact of contact lens zone geometry and ocular optics on bifocal retinal image quality." Ophthalmic and Physiological Optics 34(3): 331-345.

Brennan, N. (2015). "High myopia – Separate condition or part of a continuum?" Contact Lens and Anterior Eye 38: e1.

Brennan, N., Y. Toubouti, X. Cheng and M. Bullimore (2020). "Efficacy in myopia control." Progress in Retinal and Eye Research 83(July): 100923.

Brennan, N. A. and X. Cheng (2019). "Commonly Held Beliefs About Myopia That Lack a Robust Evidence Base." Eye & Contact Lens 45(4): 215-225.

Brennan, N. A., W. Shamp, E. Maynes, X. Cheng and M. A. Bullimore (2024). "Influence of age and race on axial elongation in myopic children: A systematic review and meta-regression." Optometry and Vision Science 101(8): 497-507.

Bullimore, M. A. (2017). "The Safety of Soft Contact Lenses in Children." Optometry & Vision Science 94(6): 638-646.

Bullimore, M. A. and N. A. Brennan (2019). "Myopia Control: Why Each Diopter Matters." Optometry & Vision Science 96(6): 463-465.

Bullimore, M. A. and N. A. Brennan (2023). "Efficacy in Myopia Control: The Low-Concentration Atropine for Myopia Progression (LAMP) Study." Ophthalmology 130(7): 771-772.

Bullimore, M. A. and N. A. Brennan (2025). "Efficacy in myopia control—The impact of rebound." Ophthalmic and Physiological Optics 45(1): 100-110.

Bullimore, M. A., N. A. Brennan and D. I. Flitcroft (2023). "The future of clinical trials of myopia control." Ophthalmic and Physiological Optics 43(3): 525-533.

Bullimore, M. A., R. E. Fusaro and C. W. Adams (1998). "The Repeatability of Automated and Clinician Refraction." Optometry and Vision Science 75(8): 617-622.

Bullimore, M. A., S. S.-Y. Lee, K. L. Schmid, J. J. Rozema, N. Leveziel, E. A. H. Mallen, N. Jacobsen, R. Iribarren, P. K. Verkicharla, J. R. Polling and P. Chamberlain (2023). "IMI—Onset and Progression of Myopia in Young Adults." Investigative Ophthalmology & Visual Science 64(6): 2.

Carroll, J. P. (1982). "Component and correlation ametropia." American journal of optometry and physiological optics 59(1): 28-33.

Chalmers, R. L., S. B. Hickson-Curran, L. Keay, W. J. Gleason and R. Albright (2015). "Rates of Adverse Events With Hydrogel and Silicone Hydrogel Daily Disposable Lenses in a Large Postmarket Surveillance Registry: The TEMPO RegistryAEs With Hydrogel and Silicone Hydrogel DD Lenses." Investigative Ophthalmology & Visual Science 56(1): 654-663.

Chalmers, R. L., L. Keay, B. Long, P. Bergenske, T. Giles and M. A. Bullimore (2010). "Risk Factors for Contact Lens Complications in US Clinical Practices." Optometry and Vision Science 87(10): 725-735.

Chalmers, R. L., L. Keay, J. McNally and J. Kern (2012). "Multicenter Case-Control Study of the Role of Lens Materials and Care Products on the Development of Corneal Infiltrates." Optometry and Vision Science 89(3): 316-325.

Chalmers, R. L., J. J. McNally, O. D. Schein, J. Katz, J. M. Tielsch, E. Alfonso, M. Bullimore, D. O'Day and J. Shovlin (2007). "Risk Factors for Corneal Infiltrates with Continuous Wear of Contact Lenses." Optometry and Vision Science 84(7): 573-579.

Chalmers, R. L., H. Wagner, G. L. Mitchell, D. Y. Lam, B. T. Kinoshita, M. E. Jansen, K. Richdale, L. Sorbara and T. T. McMahon (2011). "Age and Other Risk Factors for Corneal Infiltrative and Inflammatory Events in Young Soft Contact Lens Wearers from the Contact Lens Assessment in Youth (CLAY) Study." Investigative Ophthalmology & Visual Science 52(9): 6690-6696.

Chamberlain, P., B. Arumugam, D. Hammond and A. Bradley (2022). Assessment of MiSight 1 Day Myopia Control Treatment in Fast and Slow Progressors. American Academy of Optometry. San Diego, California.

Chamberlain, P., A. Bradley, B. Arumugam, D. Hammond, J. McNally, N. S. Logan, D. Jones, C. Ngo, S. C. Peixoto-de-Matos, C. Hunt and G. Young (2022). "Long-term Effect of Dual-focus Contact Lenses on Myopia Progression in Children: A 6-year Multicenter Clinical Trial." Optometry and Vision Science 99(3): 204-212.

Chamberlain, P., D. S. Hammond, B. Arumugam and A. Bradley (2024). "Six-year cumulative treatment effect and treatment efficacy of a dual focus myopia control contact lens." Ophthalmic and Physiological Optics 44(1): 199-205.

Chamberlain, P., P. L. d. l. Jara, B. Arumugam and M. A. Bullimore (2021). "Axial length targets for myopia control." Ophthalmic and Physiological Optics 41(3): 523-531.

Chamberlain, P., S. C. Peixoto-de-Matos, N. S. Logan, C. Ngo, D. Jones and G. Young (2019). "A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control." Optometry and Vision Science 96(8): 556-567.

Charm, J. and P. Cho (2013). "High Myopia–Partial Reduction Ortho-k: A 2-Year Randomized Study." Optometry and Vision Science 90(6): 530-539.

Charman, W. N. (2014). "Developments in the correction of presbyopia I: spectacle and contact lenses." Ophthalmic and Physiological Optics 34(1): 8-29.

Charman, W. N. and H. Radhakrishnan (2010). "Peripheral refraction and the development of refractive error: a review." Ophthalmic and Physiological Optics 30(4): 321-338.

Charman, W. N. and H. Radhakrishnan (2021). "Do optical treatments for the control of myopia progression produce proportional or absolute reductions in progression rates?" Ophthalmic and Physiological Optics 41(1): 192-197.

Chateau, N. and D. Baude (1997). "Simulated in situ optical performance of bifocal contact lenses." Optometry & Vision Science 74(7): 532-539.

Chen, C., S.-W. Cheung and P. Cho (2013). "Myopia Control Using Toric Orthokeratology (TO-SEE Study)." Investigative Opthalmology & Visual Science 54(10): 6510-6517.

Chen, J., S. Liu, Z. Zhu, G. Bulloch, T. Naduvilath, J. Wang, L. Du, J. Yang, B. Zhang, H. Zou, X. Xu and X. He (2023). "Axial length changes in progressive and non-progressive myopic children in China." Graefe's Archive for Clinical and Experimental Ophthalmology 261(5): 1493-1501.

Chen, X., Y. Guo, H. Bi, X. Liu, Y. Wu, T. Wang, L. Li, W. Lu, M. Liu and Y. Wang (2024). "The Impact of Back Optic Zone Design in Orthokeratology on Visual Performance." Translational vision science & technology 13(5): 12.

Chen, X., M. Wu, C. Yu, A. Ohlendorf, K. Rifai, C. Boeck-Maier, S. Wahl, Y. Yang, Y. Zhu, L. Li and P. Sankaridurg (2024). "Slowing myopia progression with cylindrical annular refractive elements (CARE) spectacle lenses-Year 1 results from a 2-year prospective, multi-centre trial." Acta Ophthalmologica.

Chen, Z., L. Niu, F. Xue, X. Qu, Z. Zhou, X. Zhou and R. Chu (2012). "Impact of pupil diameter on axial growth in orthokeratology." Optometry & Vision Science 89(11): 1636-1640.

Cheng, D., G. C. Woo, B. Drobe and K. L. Schmid (2014). "Effect of Bifocal and Prismatic Bifocal Spectacles on Myopia Progression in Children: Three-Year Results of a Randomized Clinical Trial." JAMA Ophthalmology 132(3): 258-264.

Cheng, K. H., S. L. Leung, H. W. Hoekman, W. H. Beekhuis, P. G. Mulder, A. J. Geerards and A. Kijlstra (1999). "Incidence of contact-lens-associated microbial keratitis and its related morbidity." Lancet 354(9174): 181-185.

Cheng, X., J. Xu and N. A. Brennan (2019). "Accommodation and its role in myopia progression and control with soft contact lenses." Ophthalmic & Physiological Optics 39(3): 162-171.

Chia, A., W.-H. Chua, Y.-B. Cheung, W.-L. Wong, A. Lingham, A. Fong and D. Tan (2012). "Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)." Ophthalmology 119(2): 347-354.

Chia, A., Q.-S. Lu and D. Tan (2016). "Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2 Myopia Control with Atropine 0.01% Eyedrops." Ophthalmology 123(2): 391-399.

Chiu, Y. C., P. C. Tsai, S. H. Lee, J. H. Wang and C. J. Chiu (2023). "Systematic Review of Myopia Progression after Cessation of Optical Interventions for Myopia Control." Journal of Clinical Medicine 13(1): 53.

Cho, P. and S. W. Cheung (2012). "Retardation of myopia in orthokeratology (ROMIO) study: A 2-year randomized clinical trial." Investigative Ophthalmology and Visual Science 53(11): 7077-7085.

Cho, P. and S. W. Cheung (2017). "Discontinuation of orthokeratology on eyeball elongation (DOEE)." Contact Lens and Anterior Eye 40(2): 82-87.

Cho, P., S. W. Cheung and M. Edwards (2005). "The Longitudinal Orthokeratology Research in Children (LORIC) in Hong Kong: A Pilot Study on Refractive Changes and Myopic Control." Current Eye Research 30(1): 71-80.

Chua, S. Y., C. Sabanayagam, Y. B. Cheung, A. Chia, R. K. Valenzuela, D. Tan, T. Y. Wong, C. Y. Cheng and S. M. Saw (2016). "Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children." Ophthalmic and Physiological Optics 36(4): 388-394.

Chung, K., N. Mohidin and D. J. O'Leary (2002). "Undercorrection of myopia enhances rather than inhibits myopia progression." Vision Research 42(22): 2555-2559.

COMET 2 Study Group (2011). "Progressive-Addition Lenses versus Single-Vision Lenses for Slowing Progression of Myopia in Children with High Accommodative Lag and Near Esophoria." Investigative Ophthalmology & Visual Science 52(5): 2749-2757.

Comet Group (2013). "Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET)." Investigative Ophthalmology & Visual Science 54(13): 7871-7884.

Cope, J. R., S. A. Collier, M. M. Rao, R. Chalmers, G. L. Mitchell, K. Richdale, H. Wagner, B. T. Kinoshita, D. Y. Lam, L. Sorbara, A. Zimmerman, J. S. Yoder and M. J. Beach (2015). "Contact Lens Wearer Demographics and Risk Behaviors for Contact Lens-Related Eye Infections--United States, 2014." MMWR Morb Mortal Wkly Rep 64(32): 865-870.

Dahlmann-Noor, A. H., D. Bokre, M. Khazova and L. L. A. Price (2025). "Measuring the visual environment of children and young people at risk of myopia: a scoping review." Graefe's Archive for Clinical and Experimental Ophthalmology.

Dart, J. K. G., C. F. Radford, D. Minassian, S. Verma and F. Stapleton (2008). "Risk factors for microbial keratitis with contemporary contact lenses: a case-control study." Ophthalmology 115(10): 1647-1654.

Dias, L., R. E. Manny, E. Weissberg and K. D. Fern (2013). "Myopia, contact lens use and self-esteem." Ophthalmic and Physiological Optics 33(5): 573-580.

Donovan, L., P. Sankaridurg, A. Ho, X. Chen, Z. Lin, V. Thomas, E. L. Smith, J. Ge and B. Holden (2012). "Myopia Progression in Chinese Children is Slower in Summer Than in Winter." Optometry and Vision Science 89(8): 1196-1202.

Donovan, L., P. Sankaridurg, A. Ho, T. Naduvilath, E. L. Smith and B. A. Holden (2012). "Myopia Progression Rates in Urban Children Wearing Single-Vision Spectacles." Optometry and Vision Science 89(1): 27-32.

Donshik, P. C., W. H. Ehlers, L. D. Anderson and J. K. Suchecki (2007). "Strategies to better engage, educate, and empower patient compliance and safe lens wear: compliance: what we know, what we do not know, and what we need to know." Eye & Contact Lens 33(6 Pt 2): 430-433.

Dumbleton, K. A., R. L. Chalmers, J. McNally, S. Bayer and D. Fonn (2002). "Effect of lens base curve on subjective comfort and assessment of fit with silicone hydrogel continuous wear contact lenses." Optometry & Vision Science 79(10): 633-637.

Edwards, M. H., R. W.-H. Li, C. S.-Y. Lam, J. K.-F. Lew and B. S.-Y. Yu (2002). "The Hong Kong progressive lens myopia control study: study design and main findings." Investigative ophthalmology & visual science 43(9): 2852-2858.

Efron, N. (2018). 18 - Daily Disposable Soft Lenses. Contact Lens Practice (Third Edition). N. Efron, Elsevier: 167-174.e161.

Efron, N. (2019). 1 - Anterior Eye Examination. Contact Lens Complications (Fourth Edition). N. Efron. Philadelphia, Elsevier: 3-23.

Efron, N. (2019). 25 - Corneal Neovascularization. Contact Lens Complications (Fourth Edition). N. Efron. Philadelphia, Elsevier: 258-268.

Efron, N. (2024). Chapter 1 - History. Contact Lens Practice (Fourth Edition). N. Efron. New Delhi, Elsevier: 2-8.e1.

Efron, N. and P. B. Morgan (2006). "Rethinking contact lens associated keratitis." Clinical and Experimental Optometry 89(5): 280-298.

Efron, N. and P. B. Morgan (2017). "Rethinking contact lens aftercare." Clinical and Experimental Optometry 100(5): 411-431.

Efron, N., P. B. Morgan and C. A. Woods (2011). "Survey of contact lens prescribing to infants, children, and teenagers." Optometry & Vision Science 88(4): 461-468.

Efron, N., P. B. Morgan, C. A. Woods, J. Santodomingo-Rubido, J. J. Nichols and T. I. C. L. P. S. Consortium (2020). "International survey of contact lens fitting for myopia control in children." Contact Lens and Anterior Eye 43(1): 4-8.

Efron, N., J. J. Nichols, C. A. Woods and P. B. Morgan (2015). "Trends in US Contact Lens Prescribing 2002 to 2014." Optometry & Vision Science 92(7): 758-767.

Escudero-Sanz, I. and R. Navarro (1999). "Off-axis aberrations of a wide-angle schematic eye model." J Opt Soc Am A Opt Image Sci Vis 16(8): 1881-1891.

Fan, D. S., C. Lai, H. H. Lau, E. Y. Cheung and D. S. Lam (2011). "Change in vision disorders among Hong Kong preschoolers in 10 years." Clinical & Experimental Ophthalmology 39(5): 398-403.

Faria-Ribeiro, M., R. Navarro and J. M. González-Méijome (2016). "Effect of Pupil Size on Wavefront Refraction during Orthokeratology." Optometry & Vision Science 93(11): 1399-1408.

Fedtke, C., K. Ehrmann and B. A. Holden (2009). "A Review of Peripheral Refraction Techniques." Optometry and Vision Science 86(5): 429-446.

Fincham, E. F. and J. Walton (1957). "The reciprocal actions of accommodation and convergence." The Journal of Physiology 137(3): 488-508.

Flitcroft, D. I. (2012). "The complex interactions of retinal, optical and environmental factors in myopia aetiology." Progress in Retinal and Eye Research 31(6): 622-660.

Flitcroft, D. I., M. He, J. B. Jonas, M. Jong, K. Naidoo, K. Ohno-Matsui, J. Rahi, S. Resnikoff, S. Vitale and L. Yannuzzi (2019). "IMI – Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies." Investigative Ophthalmology & Visual Science 60(3): M20-M30.

Fricke, T. R., M. Jong, K. S. Naidoo, P. Sankaridurg, T. J. Naduvilath, S. M. Ho, T. Y. Wong and S. Resnikoff (2018). "Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: Systematic review, meta-analysis and modelling." British Journal of Ophthalmology 102(7): 855-862.

Fricke, T. R., P. Sankaridurg, T. Naduvilath, S. Resnikoff, N. Tahhan, M. He and K. D. Frick (2023). "Establishing a method to estimate the effect of antimyopia management options on lifetime cost of myopia." British Journal of Ophthalmology 107(8): 1043-1050.

Fulk, G. W., L. A. Cyert and D. A. Parker (2002). "Seasonal variation in myopia progression and ocular elongation." Optometry & Vision Science 79(1): 46-51.

Fulk, G. W., L. A. Cyert and D. E. Parker (2000). "A Randomized Trial of the Effect of Single-Vision vs. Bifocal Lenses on Myopia Progression in Children with Esophoria." Optometry and Vision Science 77(12): 630-631.

Gantes-Nuñez, J., M. Jaskulski, N. López-Gil and P. S. Kollbaum (2023). "Optical characterisation of two novel myopia control spectacle lenses." Ophthalmic and Physiological Optics 43(3): 388-401.

Garcia-Del Valle, A. M., V. Blázquez, J. Gros-Otero, M. Infante, A. Culebras, A. Verdejo, J. Sebastián, M. García, S. Bueno and D. P. Piñero (2021). "Efficacy and safety of a soft contact lens to control myopia progression." Clinical & Experimental Optometry 104(1): 14-21.

Goss, D. A. and V. D. Cox (1985). "Trends in the change of clinical refractive error in myopes." Journal of the American Optometric Association 56(8): 608-613.

Goss, D. A. and B. B. Rainey (1998). "Relation of childhood myopia progression rates to time of year." Journal of the American Optometric Association 69(4): 262-266.

Grosvenor, T., D. M. Perrigin, J. Perrigin and B. Maslovitz (1987). "Houston Myopia Control Study: A Randomized Clinical Trial. Part II. Final Report by the Patient Care Team." Optometry and Vision Science 64(7): 482-498.

Guo, Y., M. Zhang, Y. Tong, X. Ma, S. Wang, Y. Li, Y. Du and Y. Zhou (2024). "Impact of pupil and defocus ring intersection area on retinal defocus." Ophthalmic and Physiological Optics 44(2): 472-480.

Guyatt, G., D. Sackett, J. Adachi, R. Roberts, J. Chong, D. Rosenbloom and J. Keller (1988). "A clinician's guide for conducting randomized trials in individual patients." Canadian Medical Association Journal 139(6): 497-503.

Gwiazda, J., L. Deng, R. Manny and T. T. Norton (2014). "Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial." Investigative Ophthalmology & Visual Science 55(2): 752-758.

Gwiazda, J., L. Hyman, M. Hussein, D. Everett, T. T. Norton, D. Kurtz, M. C. Leske, R. Manny, W. Marsh-Tootle and M. Scheiman (2003). "A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children." Investigative Ophthalmology & Visual Science 44(4): 1492-1500.

Hair, L. A., E. M. Steffensen and D. A. Berntsen (2021). "The Effects of Center-near and Center-distance Multifocal Contact Lenses on Peripheral Defocus and Visual Acuity." Optometry and Vision Science 98(8): 983-994.

Hardy, R., A. Hillis, D. Mutti, R. Stone, C. Taylor, L. M. Dong, M. Fazzari, J. Gwiazda, L. Hyman, T. Norton, F. Thorn, Q. Zhang, J. Gwiazda, T. Norton, K. Grice, C. Fortunato, C. Weber, A. Beale, D. Kern, S. Bittinger, D. Ghosh, R. Pacella, F. Thorn, M. C. Leske, M. Hussein, L. M. Dong, M. Fazzari, W. Hou, E. Schoenfeld, L. Dias, R. Harrison, W. Zhu, Q. Zhang, Y. Wang, A. Yassin, E. Schnall, C. Rau, J. Thomas, M. Wasserman, Y. J. Chen, S. Ahmed, L. Merill, L. Passanant, M. Rodriguez, A. Schmertz, A. Park, P. Neuschwender, G. Veeraraghavan, A. Santomarco, L. Sisti, L. Seib, D. Everett, W. Marsh-Tootle, K. Niemann, M. Frazier, C. Baldwin, C. Dillard, K. Becker, J. Raley, A. Rawden, N. Harris, T. Mars, R. Rutstein, D. Kurtz, E. Weissberg, B. Moore, E. Harb, R. Owens, S. Martin, J. Bolden, J. Smith, D. Kern, S. Bittinger, D. Ghosh, B. Jaramillo, S. Hamlett, L. Vasilakos, S. Gladstone, C. Owens, P. Kowalski, J. Hazelwood, R. Manny, C. Crossnoe, K. Fern, S. Deatherage, C. Dudonis, S. Henry, J. McLeod, M. Batres, J. Quiralte, G. Garza, G. Solis, J. Do, A. Ketcham, M. Scheiman, K. Zinzer, K. Pollack, T. Lancaster, T. Elliott, M. Bernhardt, D. Ferrara, J. Miles, S. Wilkins, R. Wilkins, J. N. Smith, D. D'Antonio, L. Lear, S. Dang, C. Sporer, M. Jameson, A. Grossman, M. Torres, H. Jones, M. Madigan-Carr, T. Sanogo and J. A. Bailey (2013). "Myopia stabilization and associated factors among participants in the correction of myopia evaluation trial (COMET)." Investigative Ophthalmology and Visual Science 54(13): 7871-7883.

Hastings, G. D., P. Tiruveedhula and A. Roorda (2024). "Wide-field optical eye models for emmetropic and myopic eyes." Journal of vision 24(7): 9.

Hayashi, K., K. Ohno-Matsui, N. Shimada, M. Moriyama, A. Kojima, W. Hayashi, K. Yasuzumi, N. Nagaoka, N. Saka, T. Yoshida, T. Tokoro and M. Mochizuki (2010). "Long-term Pattern of Progression of Myopic Maculopathy A Natural History Study." Ophthalmology 117(8): 1595-1611.e1594.

Hickson-Curran, S., G. Young, N. Brennan and C. Hunt (2016). "Chinese and Caucasian ocular topography and soft contact lens fit." Clinical and Experimental Optometry 99(2): 149-156.

Hiraoka, T., T. Kakita, F. Okamoto, H. Takahashi and T. Oshika (2012). "Long-Term Effect of Overnight Orthokeratology on Axial Length Elongation in Childhood Myopia: A 5-Year Follow-Up StudyLong-Term Effect of Orthokeratology on Axial Length." Investigative Ophthalmology & Visual Science 53(7): 3913-3919.

Holden, B. A., T. R. Fricke, D. A. Wilson, M. Jong, K. S. Naidoo, P. Sankaridurg, T. Y. Wong, T. J. Naduvilath and S. Resnikoff (2016). "Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050." Ophthalmology 123(5): 1036-1042.

Holden, B. A., D. F. Sweeney, H. A. Swarbrick, A. Vannas, K. T. Nilsson and N. Efron (1986). "The vascular response to long-term extended contact lens wear." Clinical and Experimental Optometry 69(3): 112-119.

Horner, D. G., P. S. Soni, T. O. Salmon and T. S. Swartz (1999). "Myopia progression in adolescent wearers of soft contact lenses and spectacles." Optometry & Vision Science 76(7): 474-479.

Howlett, M. H. and S. A. McFadden (2009). "Spectacle lens compensation in the pigmented guinea pig." Vision Research 49(2): 219-227.

Huang, J., D. Wen, Q. Wang, C. McAlinden, I. Flitcroft, H. Chen, S. M. Saw, H. Chen, F. Bao, Y. Zhao, L. Hu, X. Li, R. Gao, W. Lu, Y. Du, Z. Jinag, A. Yu, H. Lian, Q. Jiang, Y. Yu and J. Qu (2016). "Efficacy Comparison of 16 Interventions for Myopia Control in Children A Network Meta-analysis." Ophthalmology 123(4): 697-708.

Huang, Z., W. Zhao, Y. Z. Mao, S. Hu and C. X. Du (2023). "Factors influencing axial elongation in myopic children using overnight orthokeratology." Scientific Reports 13(1): 7715.

Hung, L. F., M. L. Crawford and E. L. Smith (1995). "Spectacle lenses alter eye growth and the refractive status of young monkeys." Nature Medicine 1(8): 761-765.

Jara, P. L. D. L., P. Sankaridurg, A. Ho, A. Martinez, L. Donovan, E. L. S. III, X. Chen, J. Ge, B. Holden and T. V. C. M. C. S. Group (2010). "A Silicone Hydrogel Contact Lens Produced Less Myopia Progression Than Single Vision Spectacles in Chinese Children Over a 6 Month Period." Investigative Ophthalmology & Visual Science 51(13): 2198-2198.

Jawaid, I., K. Saunders, C. J. Hammond, A. Dahlmann-Noor and M. A. Bullimore (2024). "Low concentration atropine and myopia: a narrative review of the evidence for United Kingdom based practitioners." Eye 38(3): 434-441.

Ji, Q., Y. S. Yoo, H. Alam and G. Yoon (2018). "Through-focus optical characteristics of monofocal and bifocal soft contact lenses across the peripheral visual field." Ophthalmic and Physiological Optics 38(3): 326-336.

Jones-Jordan, L. A., L. T. Sinnott, R. H. Chu, S. A. Cotter, R. N. Kleinstein, R. E. Manny, D. O. Mutti, J. D. Twelker, K. Zadnik and C. S. Group (2021). "Myopia Progression as a Function of Sex, Age, and Ethnicity." Investigative Ophthalmology & Visual Science 62(10): 36.

Jones, J. H., D. O. Mutti, L. A. Jones-Jordan and J. J. Walline (2022). "Effect of Combining 0.01% Atropine with Soft Multifocal Contact Lenses on Myopia Progression in Children." Optometry and Vision Science 99(5): 434-442.

Jones, L. A., G. L. Mitchell, D. O. Mutti, J. R. Hayes, M. L. Moeschberger and K. Zadnik (2005). "Comparison of Ocular Component Growth Curves among Refractive Error Groups in Children." Investigative Ophthalmology & Visual Science 46(7): 2317-2327.

Jung, S.-K., J. H. Lee, H. Kakizaki and D. Jee (2012). "Prevalence of Myopia and its Association with Body Stature and Educational Level in 19-Year-Old Male Conscripts in Seoul, South Korea." Investigative Opthalmology & Visual Science 53(9): 5579.

Kakita, T., T. Hiraoka and T. Oshika (2016). "Influence of Overnight Orthokeratology on Axial Elongation in Childhood Myopia." Investigative Ophthalmology & Visual Science 52(5): 2170-2174.

Kasthurirangan, S. and A. Glasser (2005). "Characteristics of pupil responses during far-to-near and near-to-far accommodation." Ophthalmic and Physiological Optics 25(4): 328-339.

Keay, L., K. Edwards, T. Naduvilath, K. Forde and F. Stapleton (2006). "Factors affecting the morbidity of contact lens-related microbial keratitis: a population study." Investigative Ophthalmology & Visual Science 47(10): 4302-4308.

Keay, L., F. Stapleton and O. Schein (2007). "Epidemiology of Contact Lens–Related Inflammation and Microbial Keratitis: A 20-year Perspective." Eye & Contact Lens 33(6, Part 2 of 2): 346-353.

Kent, D. M., E. Steyerberg and D. van Klaveren (2018). "Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects." British Medical Journal 363: k4245.

Komarova, N. (2006). "Stochastic modeling of drug resistance in cancer." Journal of Theoretical Biology 239(3): 351-366.

Koomson, N. Y., A. O. Amedo, C. Opoku-Baah, P. B. Ampeh, E. Ankamah and K. Bonsu (2016). "Relationship between Reduced Accommodative Lag and Myopia Progression." Optometry and Vision Science 93(7): 683-691.

Kotz, D. and R. West (2022). "Key concepts in clinical epidemiology: addressing and reporting sources of bias in randomized controlled trials." Journal of Clinical Epidemiology 143: 197-201.

Kristman, V., M. Manno and P. Côté (2004). "Loss to Follow-Up in Cohort Studies: How Much is Too Much?" European Journal of Epidemiology 19(8): 751-760.

Lam, A. K., R. Chan and P. C. Pang (2001). "The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster." Ophthalmic & Physiological Optics 21(6): 477-483.

Lam, C. S. Y., W. C. Tang, P. H. Lee, H. Y. Zhang, H. Qi, K. Hasegawa and C. H. To (2022). "Myopia control effect of defocus incorporated multiple segments (DIMS) spectacle lens in Chinese children: results of a 3-year follow-up study." British Journal of Ophthalmology 106(8): 1110-1114.

Lam, C. S. Y., W. C. Tang, D. Y.-y. Tse, R. P. K. Lee, R. K. M. Chun, K. Hasegawa, H. Qi, T. Hatanaka and C. H. To (2019). "Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial." British Journal of Ophthalmology 104(3): 363-368.

Lam, C. S. Y., W. C. Tang, D. Y. Y. Tse, Y. Y. Tang and C. H. To (2014). "Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: A 2-year randomised clinical trial." British Journal of Ophthalmology 98(1): 40-45.

Lam, C. S. Y., W. C. Tang, H. Y. Zhang, P. H. Lee, D. Y. Y. Tse, H. Qi, N. Vlasak and C. H. To (2023). "Long-term myopia control effect and safety in children wearing DIMS spectacle lenses for 6 years." Scientific Reports 13(1): 5475.

Lam, D. Y., B. T. Kinoshita, M. E. Jansen, G. L. Mitchell, R. L. Chalmers, T. T. McMahon, K. Richdale, L. Sorbara, H. Wagner and C. S. Group (2011). "Contact Lens Assessment in Youth: Methods and Baseline Findings." Optometry and Vision Science 88(6): 708-715.

Langenbucher, A., S. Goebels, N. Szentmáry, B. Seitz and T. Eppig (2013). "Vignetting and Field of View with the KAMRA Corneal Inlay." BioMed Research International 2013: 154593.

Laughton, D., J. S. Hill, M. McParland, V. Tasso, J. Woods, X. Zhu, G. Young, R. Craven, C. Hunt, J. Neitz, M. Neitz, T. W. Chalberg, D. Jones and J. S. Wolffsohn (2024). "Control of myopia using diffusion optics spectacle lenses: 4-year results of a multicentre randomised controlled, efficacy and safety study (CYPRESS)." BMJ Open Ophthalmology 9(1): e001790.

Lawrenson, J. G., R. Shah, B. Huntjens, L. E. Downie, G. Virgili, R. Dhakal, P. K. Verkicharla, D. Li, S. Mavi, A. Kernohan, T. Li and J. J. Walline (2023). "Interventions for myopia control in children: a living systematic review and network meta-analysis." Cochrane Database of Systematic Reviews 2023(2).

Lazar, R., J. Degen, A. S. Fiechter, A. Monticelli and M. Spitschan (2024). "Regulation of pupil size in natural vision across the human lifespan." Royal Society Open Science 11(6): 191613.

Li, S. M., M. T. Kang, S. S. Wu, L. R. Liu, H. Li, Z. Chen and N. Wang (2016). "Efficacy, Safety and Acceptability of Orthokeratology on Slowing Axial Elongation in Myopic Children by Meta-Analysis." Current Eye Research 41(5): 600-608.

LI, X., Y. Huang, C. Liu, Z. Yin, Z. Cui, E. W. Lim, B. Drobe, H. Chen and J. Bao (2024). "Myopia control efficacy of Spectacle Lenses with Highly Aspherical Lenslets: results of a 5-year follow-up study." Investigative Ophthalmology & Visual Science 65(7): 131.

Li, X., Y. Huang, Z. Yin, C. Liu, S. Zhang, A. Yang, B. Drobe, H. Chen and J. Bao (2023). "Myopia Control Efficacy of Spectacle Lenses With Aspherical Lenslets: Results of a 3-Year Follow-Up Study." Am J Ophthalmol 253: 160-168.

Lin, L. L., Y. F. Shih, C. K. Hsiao and C. J. Chen (2004). "Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000." Ann Acad Med Singapore 33(1): 27-33.

Lippman, J. I. (1990). "Contact lens materials: a critical review." Contact Lens Association of Ophthalmologists Journal 16(4): 287-291.

Liu, Y. and C. Wildsoet (2011). "The Effect of Two-Zone Concentric Bifocal Spectacle Lenses on Refractive Error Development and Eye Growth in Young Chicks." Investigative Ophthalmology & Visual Science 52(2): 1078-1086.

Liu, Y. and C. Wildsoet (2012). "The effective add inherent in 2-zone negative lenses inhibits eye growth in myopic young chicks." Investigative Ophthalmology and Visual Science 53(8): 5085-5093.

Ma, Y., X. Qu, X. Zhu, X. Xu, J. Zhu, P. Sankaridurg, S. Lin, L. Lu, R. Zhao, L. Wang, H. Shi, H. Tan, X. You, H. Yuan, S. Sun, M. Wang, X. He, H. Zou and N. Congdon (2016). "Age-Specific Prevalence of Visual Impairment and Refractive Error in Children Aged 3–10 Years in Shanghai, China." Investigative Opthalmology & Visual Science 57(14): 6188-6196.

Maldonado-Codina, C. (2024). Chapter 4 - Soft Lens Materials. Contact Lens Practice (Fourth Edition). N. Efron. New Delhi, Elsevier: 46-62.e42.

Mariotti, S., I. Kocur, S. Resnikoff, m. jong, K. Naidoo, M. He, B. Holden, S. Salomão, P. Sankaridurg, J. Jonas, S. Saw, E. Iii, J. Kedir, K. Trier, T. Y. Wong, H. Minto, A. Yekta, S. Vitale and J. Zhao (2015). The impact of myopia and high myopia. Report of the Joint World Health Organization-Brien Holden Vision Institute Global Scientific Meeting on Myopia.

Mathur, A., D. A. Atchison and D. H. Scott (2008). "Ocular aberrations in the peripheral visual field." Optics Letters 33(8): 863-865.

Mathur, A., J. Gehrmann and D. A. Atchison (2013). "Pupil shape as viewed along the horizontal visual field." Journal of Vision 13(6).

McCullough, S. J., L. O'Donoghue and K. J. Saunders (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, S. A., D. Y. Tse, H. E. Bowrey, A. J. Leotta, C. S. Lam, C. F. Wildsoet and C. H. To (2014). "Integration of defocus by dual power fresnel lenses inhibits myopia in the mammalian eye." Investigative Ophthalmology and Visual Science 55(2): 908-917.

Mirshahi, A., K. A. Ponto, R. Hoehn, I. Zwiener, T. Zeller, K. Lackner, M. E. Beutel and N. Pfeiffer (2014). "Myopia and Level of Education Results from the Gutenberg Health Study." Ophthalmology 121(10): 2047-2052.

Morgan, I. G. and K. A. Rose (2013). "Myopia and international educational performance." Ophthalmic & Physiological Optics 33(3): 329-338.

Morgan, P. B. and N. Efron (2002). "Comparative clinical performance of two silicone hydrogel contact lenses for continuous wear." Clinical & Experimental Optometry 85(3): 183-192.

Morgan, P. B., N. Efron, N. A. Brennan, E. A. Hill, M. K. Raynor and A. B. Tullo (2005). "Risk Factors for the Development of Corneal Infiltrative Events Associated with Contact Lens Wear." Investigative Opthalmology & Visual Science 46(9): 3136-3143.

Morgan, P. B., N. Efron, E. A. Hill, M. K. Raynor, M. A. Whiting and A. B. Tullo (2005). "Incidence of keratitis of varying severity among contact lens wearers." British Journal of Ophthalmology 89(4): 430-436.

Mori, K., H. Torii, Y. Hara, M. Hara, E. Yotsukura, A. Hanyuda, K. Negishi, T. Kurihara and K. Tsubota (2021). "Effect of Violet Light-Transmitting Eyeglasses on Axial Elongation in Myopic Children: A Randomized Controlled Trial." Journal of Clinical Medicine 10(22): 5462.

Mountjoy, E., N. M. Davies, D. Plotnikov, G. D. Smith, S. Rodriguez, C. E. Williams, J. A. Guggenheim and D. Atan (2018). "Education and myopia: assessing the direction of causality by mendelian randomisation." British Medical Journal 361: k2022.

Mutti, D. O., J. R. Hayes, G. L. Mitchell, L. A. Jones, M. L. Moeschberger, S. A. Cotter, R. N. Kleinstein, R. E. Manny, J. D. Twelker and K. Zadnik (2007). "Refractive Error, Axial Length, and Relative Peripheral Refractive Error before and after the Onset of Myopia." Investigative ophthalmology & visual science 48(6): 2510-2519.

Mutti, D. O., G. L. Mitchell, J. R. Hayes, L. A. Jones, M. L. Moeschberger, S. A. Cotter, R. N. Kleinstein, R. E. Manny, J. D. Twelker and K. Zadnik (2006). "Accommodative lag before and after the onset of myopia." Investigative Ophthalmology & Visual Science 47(3): 837-846.

Mutti, D. O., R. I. Sholtz, N. E. Friedman and K. Zadnik (2000). "Peripheral refraction and ocular shape in children." Investigative Opthalmology & Visual Science 41(5): 1022-1030.

Mutti, D. O., L. T. Sinnott, N. A. Brennan, X. Cheng and K. Zadnik (2022). "The Limited Value of Prior Change in Predicting Future Progression of Juvenile-onset Myopia." Optometry & Vision Science 99(5): 424-433.

Mutti, D. O., L. T. Sinnott, G. Lynn Mitchell, L. A. Jordan, N. E. Friedman, S. L. Frane and W. K. Lin (2018). "Ocular Component Development during Infancy and Early Childhood." Optometry & Vision Science 95(11): 976-985.

Mutti, D. O., L. T. Sinnott, G. L. Mitchell, L. A. Jones-Jordan, M. L. Moeschberger, S. A. Cotter, R. N. Kleinstein, R. E. Manny, J. D. Twelker, K. Zadnik and C. S. Group (2011). "Relative Peripheral Refractive Error and the Risk of Onset and Progression of Myopia in Children." Investigative Opthalmology & Visual Science 52(1): 199-205.

Mutti, D. O., L. T. Sinnott, K. Zadnik, f. t. B. S. G. Group and C. S. the (2023). "Compensation for Vitreous Chamber Elongation in Infancy and Childhood." Optometry and Vision Science 100(1): 43-51.

Nakatsuka, C., S. Hasebe, F. Nonaka and H. Ohtsuki (2005). "Accommodative lag under habitual seeing conditions: comparison between myopic and emmetropic children." Japanese Journal of Ophthalmology 49(3): 189-194.

Neitz, J. and M. Neitz (2024). "Diffusion Optics Technology (DOT): A Myopia Control Spectacle Lens Based on Contrast Theory." Translational Vision Science & Technology 13(10): 42.

Norton, T. T. and J. T. Siegwart (2013). "Light levels, refractive development, and myopia – A speculative review." Experimental Eye Research 114: 48-57.

Papas, E. B., C. M. Vajdic, R. Austen and B. A. Holden (1997). "High-oxygen-transmissibility soft contact lenses do not induce limbal hyperaemia." Current Eye Research 16(9): 942-948.

Park, S. J., N.-K. Choi, N.-K. Choi, K. H. Park and S. J. Woo (2013). "Five Year Nationwide Incidence of Rhegmatogenous Retinal Detachment Requiring Surgery in Korea." PLoS ONE 8(11): e80174.

Pärssinen, O., E. Hemminki and A. Klemetti (1989). "Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren." British Journal of Ophthalmology 73(7): 547-551.

Pärssinen, O., M. Kauppinen and A. Viljanen (2014). "The progression of myopia from its onset at age 8–12 to adulthood and the influence of heredity and external factors on myopic progression. A 23-year follow-up study." Acta Ophthalmologica 92(8): 730-739.

Pauné, J., H. Morales, J. Armengol, L. Quevedo, M. Faria-Ribeiro and J. M. González-Méijome (2015). "Myopia Control with a Novel Peripheral Gradient Soft Lens and Orthokeratology: A 2-Year Clinical Trial." BioMed Research International 2015(D): 507572.

Peng, W., Z. Zhang, F. Wang, S. Sun and Y. Sun (2023). "Association of educational environment with the prevalence of myopia: a cross-sectional study in central China." Front Public Health 11: 1188198.

Phillips, J. R. (2005). "Monovision slows juvenile myopia progression unilaterally." British Journal of Ophthalmology 89(9): 1196-1200.

Plowright, A. J., C. Maldonado-Codina, G. F. Howarth, J. Kern and P. B. Morgan (2015). "Daily Disposable Contact Lenses versus Spectacles in Teenagers." Optometry and Vision Science 92(1): 44-52.

Poggio, E. C., R. J. Glynn, O. D. Schein, J. M. Seddon, M. J. Shannon, V. A. Scardino and K. R. Kenyon (1989). "The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses." New England Journal of Medicine 321(12): 779-783.

Polling, J. R., E. Tan, S. Driessen, S. E. Loudon, H. L. Wong, A. van der Schans, J. W. L. Tideman and C. C. W. Klaver (2020). "A 3-year follow-up study of atropine treatment for progressive myopia in Europeans." Eye 34(11): 2020-2028.

Pope, J. M., P. K. Verkicharla, F. Sepehrband, M. Suheimat, K. L. Schmid and D. A. Atchison (2017). "Three-dimensional MRI study of the relationship between eye dimensions, retinal shape and myopia." Biomedical Optics Express 8(5): 2386-2395.

Qin, Z., T. Peng, Z. Zhang, J. Lou, C. Wang, R. Deng, M. Xu, X. Yu and W. Chen (2022). "Myopia progression and stabilization in school-aged children with single-vision lenses." Acta Ophthalmologica 100(4): e950-e956.

Rah, M. J., J. J. Walline, L. A. Jones-Jordan, L. T. Sinnott, J. M. Jackson, R. E. Manny, B. Coffey, S. Lyons and A. S. Group (2010). "Vision Specific Quality of Life of Pediatric Contact Lens Wearers." Optometry and Vision Science 87(8): 560-566.

Ramsdale, C. and W. N. Charman (1988). "Accommodation and convergence: effects of lenses and prisms in 'closed-loop' conditions." Ophthalmic & Physiological Optics 8(1): 43-52.

Rappon, J., C. Chung, G. Young, C. Hunt, J. Neitz, M. Neitz and T. Chalberg (2023). "Control of myopia using diffusion optics spectacle lenses: 12-month results of a randomised controlled, efficacy and safety study (CYPRESS)." British Journal of Ophthalmology 107(11): 1709-1715.

Remón, L., P. Pérez-Merino, R. J. Macedo-de-Araújo, A. I. Amorim-de-Sousa and J. M. González-Méijome (2020). "Bifocal and Multifocal Contact Lenses for Presbyopia and Myopia Control." Journal of Ophthalmology 2020: 8067657.

Rose, K. A., I. G. Morgan, J. Ip, A. Kifley, S. Huynh, W. Smith and P. Mitchell (2008). "Outdoor Activity Reduces the Prevalence of Myopia in Children." Ophthalmology 115(8): 1279-1285.

Rozema, J., S. Dankert and R. Iribarren (2023). "Emmetropization and nonmyopic eye growth." Survey of Ophthalmology 68(4): 759-783.

Rozema, J., S. Dankert, R. Iribarren, C. Lanca and S.-M. Saw (2019). "Axial Growth and Lens Power Loss at Myopia Onset in Singaporean Children." Investigative Ophthalmology & Visual Science 60(8): 3091-3099.

Rudnicka, A. R., V. V. Kapetanakis, A. K. Wathern, N. S. Logan, B. Gilmartin, P. H. Whincup, D. G. Cook and C. G. Owen (2016). "Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention." British journal of ophthalmology 100(7): 882-890.

Sah, R. P., M. Jaskulski and P. S. Kollbaum (2022). "Modelling the refractive and imaging impact of multi-zone lenses utilised for myopia control in children's eyes." Ophthalmic & Physiological Optics 42(3): 571-585.

Sah, R. P., D. Meyer, M. Jaskulski, M. Rickert, X. Cheng, N. Brennan and P. S. Kollbaum (2023). "Impact of zone geometry on the introduction of myopic defocus in young adult eyes wearing multi-zone lenses." Ophthalmic & Physiological Optics 43(5): 1110-1124.

Sánchez-Tena, M. Á., A. Ballesteros-Sánchez, C. Martinez-Perez, C. Alvarez-Peregrina, C. De-Hita-Cantalejo, M. C. Sánchez-González and J. M. Sánchez-González (2024). "Assessing the rebound phenomenon in different myopia control treatments: A systematic review." Ophthalmic and Physiological Optics 44(2): 270-279.

Sankaridurg, P., R. C. Bakaraju, T. Naduvilath, X. Chen, R. Weng, D. Tilia, P. Xu, W. Li, F. Conrad, E. L. Smith and K. Ehrmann (2019). "Myopia control with novel central and peripheral plus contact

lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial." Ophthalmic and Physiological Optics 39(4): 294-307.

Sankaridurg, P., L. Donovan, S. Varnas, A. Ho, X. Chen, A. Martinez, S. Fisher, Z. Lin, E. L. Smith, J. Ge and B. Holden (2010). "Spectacle Lenses Designed to Reduce Progression of Myopia: 12-Month Results." Optometry and Vision Science 87(9): 631-641.

Sankaridurg, P., B. Holden, E. Smith, T. Naduvilath, X. Chen, P. L. d. l. Jara, A. Martinez, J. Kwan, A. Ho, K. Frick and J. Ge (2011). "Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results." Investigative Ophthalmology & Visual Science 52(13): 9362-9367.

Sankaridurg, P., B. A. Holden, L. A. Donovan, C.-h. To, W. H. Chua, L. Li and X. Chen (2014). "An Annual Rate of Myopic Progression Model for Asian children." Investigative Ophthalmology & Visual Science 55(13): 3629-3629.

Santodomingo-Rubido, J., C. Villa-Collar, B. Gilmartin and R. Gutiérrez-Ortega (2012). "Myopia Control with Orthokeratology Contact Lenses in Spain: Refractive and Biometric ChangesOrthokeratology in Myopia Progression Control." Investigative Ophthalmology & Visual Science 53(8): 5060-5065.

Schaeffel, F., A. Glasser and H. C. Howland (1988). "Accommodation, refractive error and eye growth in chickens." Vision Research 28(5): 639-657.

Schein, O. D., J. J. McNally, J. Katz, R. L. Chalmers, J. M. Tielsch, E. Alfonso, M. Bullimore, D. O'Day and J. Shovlin (2005). "The Incidence of Microbial Keratitis among Wearers of a 30-Day Silicone Hydrogel Extended-Wear Contact Lens." Ophthalmology 112(12): 2172-2179.

Scott, R. and T. Grosvenor (1993). "Structural model for emmetropic and myopic eyes." Ophthalmic & Physiological Optics 13(1): 41-47.

Senn, S. (2004). "Individual response to treatment: is it a valid assumption?" British Medical Journal 329(7472): 966-968.

Shaikh, A. W., J. T. Siegwart, Jr. and T. T. Norton (1999). "Effect of interrupted lens wear on compensation for a minus lens in tree shrews." Optometry & Vision Science 76(5): 308-315.

Silbert, J., N. Matta, J. Tian, E. Singman and D. I. Silbert (2013). "Pupil size and anisocoria in children measured by the plusoptiX photoscreener." Journal of American Association for Pediatric Ophthalmology and Strabismus 17(6): 609-611.

Sindt, C. W. and C. M. Riley (2011). "Practitioner attitudes on children and contact lenses." Optometry 82(1): 44-45.

Singh, N. K., M. Jaskulski, V. Ramasubramanian, D. Meyer, O. Reed, M. E. Rickert, A. Bradley and P. S. Kollbaum (2019). "Validation of a Clinical Aberrometer Using Pyramidal Wavefront Sensing." Optometry and Vision Science 96(10): 733-744.

Smith, E. L., 3rd (2011). "Prentice Award Lecture 2010: A case for peripheral optical treatment strategies for myopia." Optometry & Vision Science 88(9): 1029-1044.

Smith, E. L., 3rd, B. Arumugam, L. F. Hung, Z. She, K. Beach and P. Sankaridurg (2020). "Eccentricity-dependent effects of simultaneous competing defocus on emmetropization in infant rhesus monkeys." Vision Research 177: 32-40.

Smith, E. L., 3rd and L. F. Hung (1999). "The role of optical defocus in regulating refractive development in infant monkeys." Vision Research 39(8): 1415-1435.

Smith, E. L., 3rd, C. S. Kee, R. Ramamirtham, Y. Qiao-Grider and L. F. Hung (2005). "Peripheral vision can influence eye growth and refractive development in infant monkeys." Investigative Ophthalmology & Visual Science 46(11): 3965-3972.

Smotherman, C., N. A. Brennan, X. Cheng, W. Shamp, R. Butterfield and M. A. Bullimore (2023). "Influence of age and race on refractive error progression in myopic children." Investigative Ophthalmology & Visual Science 64(8): 811-811.

So, C., J. Lian, S. M. McGhee, R. W. M. Sum, A. K. C. Lam and M. K. H. Yap (2024). "Lifetime cost-effectiveness of myopia control intervention for the children population." Journal of Global Health 14: 04183.

Stapleton, F., M. Bakkar, N. Carnt, R. Chalmers, A. K. Vijay, S. Marasini, A. Ng, J. Tan, H. Wagner, C. Woods and J. S. Wolffsohn (2021). "CLEAR - Contact lens complications." Contact Lens and Anterior Eye 44(2): 330-367.

Stapleton, F., L. Keay, K. Edwards, T. Naduvilath, J. K. G. Dart, G. Brian and B. A. Holden (2008). "The incidence of contact lens-related microbial keratitis in Australia." Ophthalmology 115(10): 1655-1662.

Su, B., P. Cho, S. J. Vincent, J. Zheng, J. Chen, C. Ye, T. Wang, J. Zhang, K. Zhang, F. Lu and J. Jiang (2024). "Novel Lenslet-ARray-Integrated Spectacle Lenses for Myopia Control: A 1-Year Randomized, Double-Masked, Controlled Trial." Ophthalmology 131(12): 1389-1397.

Swarbrick, H. A., A. Alharbi, K. Watt, E. Lum and P. Kang (2015). "Myopia control during orthokeratology lens wear in children using a novel study design." Ophthalmology 122(3): 620-630.

Szczotka-Flynn, L., Y. Jiang, S. Raghupathy, R. A. Bielefeld, M. T. Garvey, M. R. Jacobs, J. Kern and S. M. Debanne (2014). "Corneal Inflammatory Events with Daily Silicone Hydrogel Lens Wear." Optometry and Vision Science 91(1): 3-12.

Tan, Q., A. L. Ng, G. P. Cheng, V. C. Woo and P. Cho (2023). "Combined 0.01% atropine with orthokeratology in childhood myopia control (AOK) study: A 2-year randomized clinical trial." Contact Lens and Anterior Eye 46(1): 101723.

Tanner, J. and N. Efron (2018). 19 - Reusable Soft Lenses. Contact Lens Practice (Third Edition). N. Efron, Elsevier: 175-186.e171.

Terry, R. L., C. M. Schnider, B. A. Holden, R. Cornish, T. Grant, D. Sweeney, D. La Hood and A. Back (1993). "CCLRU standards for success of daily and extended wear contact lenses." Optometry & Vision Science 70(3): 234-243.

Theophanous, C., B. S. Modjtahedi, M. Batech, D. S. Marlin, T. Q. Luong and D. S. Fong (2018). "Myopia prevalence and risk factors in children." Clinical Ophthalmology (Auckland, N.Z.) 12: 1581-1587.

Tong, L., X. L. Huang, A. L. T. Koh, X. Zhang, D. T. H. Tan and W.-H. Chua (2009). "Atropine for the Treatment of Childhood Myopia: Effect on Myopia Progression after Cessation of Atropine." Ophthalmology 116(3): 572-579.

Torii, H., T. Kurihara, Y. Seko, K. Negishi, K. Ohnuma, T. Inaba, M. Kawashima, X. Jiang, S. Kondo, M. Miyauchi, Y. Miwa, Y. Katada, K. Mori, K. Kato, K. Tsubota, H. Goto, M. Oda, M. Hatori and K. Tsubota (2017). "Violet Light Exposure Can Be a Preventive Strategy Against Myopia Progression." EBioMedicine 15: 210-219.

Tricard, D., S. Marillet, P. Ingrand, M. A. Bullimore, R. R. A. Bourne and N. Leveziel (2022). "Progression of myopia in children and teenagers: a nationwide longitudinal study." British Journal of Ophthalmology 106(8): 1104-1109.

Tsai, T.-H., Y.-L. Liu, I. H. Ma, C.-C. Su, C.-W. Lin, L. L.-K. Lin, C. K. Hsiao and I. J. Wang (2021). "Evolution of the Prevalence of Myopia among Taiwanese Schoolchildren A Review of Survey Data from 1983 through 2017." Ophthalmology 128(2): 290-301.

Tse, D. Y., C. S. Lam, J. A. Guggenheim, C. Lam, K.-k. Li, Q. Liu and C.-h. To (2007). "Simultaneous Defocus Integration during Refractive Development." Investigative Ophthalmology & Visual Science 48(12): 5352-5359.

Vaidyanathan, U., G. C. Hopping, H. Y. Liu, A. N. Somani, Y. C. Ronquillo, P. C. Hoopes and M. Moshirfar (2019). "Persistent Corneal Epithelial Defects: A Review Article." Med Hypothesis Discov Innov Ophthalmol 8(3): 163-176.

Verkicharla, P. K., P. Kammari and A. V. Das (2020). "Myopia progression varies with age and severity of myopia." PLOS ONE 15(11): e0241759.

Verkicharla, P. K., A. Mathur, E. A. Mallen, J. M. Pope and D. A. Atchison (2012). "Eye shape and retinal shape, and their relation to peripheral refraction." Ophthalmic & Physiological Optics 32(3): 184-199.

Verkicharla, P. K., K. Ohno-Matsui and S. M. Saw (2015). "Current and predicted demographics of high myopia and an update of its associated pathological changes." Ophthalmic and Physiological Optics 35(5): 465-475.

Vitale, S., L. Ellwein, M. F. Cotch, F. L. Ferris and R. Sperduto (2008). "Prevalence of Refractive Error in the United States, 1999-2004." Archives of Ophthalmology 126(8): 1111-1119.

Vongphanit, J., P. Mitchell and J. J. Wang (2002). "Prevalence and progression of myopic retinopathy in an older population." Ophthalmology 109(4): 704-711.

Wagner, H., R. L. Chalmers, G. L. Mitchell, M. E. Jansen, B. T. Kinoshita, D. Y. Lam, T. T. McMahon, K. Richdale, L. Sorbara and C. S. Group (2011). "Risk Factors for Interruption to Soft Contact Lens Wear in Children and Young Adults." Optometry and Vision Science 88(8): 973-980.

Walline, J. J., K. L. Greiner, M. E. McVey and L. A. Jones-Jordan (2013). "Multifocal Contact Lens Myopia Control." Optometry and Vision Science 90(11): 1207-1214.

Walline, J. J., L. A. Jones, L. Sinnott, M. Chitkara, B. Coffey, J. M. Jackson, R. E. Manny, M. J. Rah, M. J. Prinstein and A. S. Group (2009). "Randomized Trial of the Effect of Contact Lens Wear on Self-Perception in Children." Optometry and Vision Science 86(3): 222-232.

Walline, J. J., L. A. Jones, L. Sinnott, R. E. Manny, A. Gaume, M. J. Rah, M. Chitkara, S. Lyons and A. S. Group (2008). "A Randomized Trial of the Effect of Soft Contact Lenses on Myopia Progression in Children." Investigative Opthalmology & Visual Science 49(11): 4702-4706.

Walline, J. J., L. A. Jones and L. T. Sinnott (2009). "Corneal reshaping and myopia progression." British Journal of Ophthalmology 93(9): 1181.

Walline, J. J., M. W. Robboy, G. Hilmantel, M. E. Tarver, N. A. Afshari, D. K. Dhaliwal, C. L. Morse, C. J. Quinn, M. X. Repka and M. B. Eydelman (2018). "Food and Drug Administration, American Academy of Ophthalmology, American Academy of Optometry, American Association for Pediatric Ophthalmology and Strabismus, American Optometric Association, American Society of Cataract and Refractive Surgery, and Contact Lens Association of Ophthalmologists Co-Sponsored Workshop." Eye & Contact Lens 44(4): 205-211.

Walline, J. J., M. K. Walker, D. O. Mutti, L. A. Jones-Jordan, L. T. Sinnott, A. G. Giannoni, K. M. Bickle, K. L. Schulle, A. Nixon, G. E. Pierce, D. A. Berntsen and B. S. Group (2020). "Effect of High Add Power, Medium Add Power, or Single-Vision Contact Lenses on Myopia Progression in Children." JAMA 324(6): 571-580.

Wallman, J. and J. Winawer (2004). "Homeostasis of eye growth and the question of myopia." Neuron 43(4): 447-468.

Walther, G., D. Meyer, J. Richards, M. Rickert and P. Kollbaum (2024). "On-eye centration of soft contact lenses." Ophthalmic and Physiological Optics 44(4): 737-745.

Wang, J., D. Yang, H. Bi, B. Du, W. Lin, T. Gu, B. Zhang and R. Wei (2018). "A New Method to Analyze the Relative Corneal Refractive Power and Its Association to Myopic Progression Control With Orthokeratology." Transl Vis Sci Technol 7(6): 17.

Wang, L., S. González, W. Dai, S. Deng and L. Lu (2016). "Effect of Hypoxia-regulated Polo-like Kinase 3 (Plk3) on Human Limbal Stem Cell Differentiation." J Biol Chem 291(32): 16519-16529.

Watson, A. B. and J. I. Yellott (2012). "A unified formula for light-adapted pupil size." Journal of Vision 12(10): 12.

Wiesel, T. N. and E. Raviola (1977). "Myopia and eye enlargement after neonatal lid fusion in monkeys." Nature 266(5597): 66-68.

Wildsoet, C. and J. Wallman (1995). "Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks." Vision Research 35(9): 1175-1194.

Wildsoet, C. F. and K. L. Schmid (2001). "Emmetropization in chicks uses optical vergence and relative distance cues to decode defocus." Vision Res 41(24): 3197-3204.

Winn, B., D. Whitaker, D. B. Elliott and N. J. Phillips (1994). "Factors affecting light-adapted pupil size in normal human subjects." Investigative Ophthalmology & Visual Science 35(3): 1132-1137.

Wolffsohn, J. S., A. Calossi, P. Cho, K. Gifford, L. Jones, D. Jones, S. Guthrie, M. Li, C. Lipener, N. S. Logan, F. Malet, S. C. Peixoto-de-Matos, J. M. González-Méijome, J. J. Nichols, J. B. Orr, J. Santodomingo-Rubido, T. Schaefer, N. Thite, E. v. d. Worp, E. Tarutta, E. Iomdina, B. M. Ali, C. Villa-Collar, C. Abesamis-Dichoso, C. Chen, H. Pult, P. Blaser, G. P. S. Johanna, F. Iqbal, R. Ramos, G. C. Orihuela and N. Boychev (2020). "Global trends in myopia management attitudes and strategies in clinical practice – 2019 Update." Contact Lens and Anterior Eye 43(1): 9-17.

Wolffsohn, J. S., A. Calossi, P. Cho, K. Gifford, L. Jones, M. Li, C. Lipener, N. S. Logan, F. Malet, S. Matos, J. M. G. Meijome, J. J. Nichols, J. B. Orr, J. Santodomingo-Rubido, T. Schaefer, N. Thite, E. v. d. Worp and M. Zvirgzdina (2016). "Global trends in myopia management attitudes and strategies in clinical practice." Contact Lens and Anterior Eye 39(2): 106-116.

Wolffsohn, J. S., D. I. Flitcroft, K. L. Gifford, M. Jong, L. Jones, C. C. W. Klaver, N. S. Logan, K. Naidoo, S. Resnikoff, P. Sankaridurg, E. L. Smith, D. Troilo and C. F. Wildsoet (2019). "IMI – Myopia Control Reports Overview and Introduction." Investigative Ophthalmology & Visual Science 60(3): M1-M19.

Wolffsohn, J. S., P. S. Kollbaum, D. A. Berntsen, D. A. Atchison, A. Benavente, A. Bradley, H. Buckhurst, M. Collins, T. Fujikado, T. Hiraoka, M. Hirota, D. Jones, N. S. Logan, L. Lundström, H. Torii, S. A. Read and K. Naidoo (2019). "IMI – Clinical Myopia Control Trials and Instrumentation Report." Investigative Opthalmology & Visual Science 60(3): M132-M160.

Wong, H.-B., D. Machin, S.-B. Tan, T.-Y. Wong and S.-M. Saw (2010). "Ocular Component Growth Curves among Singaporean Children with Different Refractive Error Status." Investigative Ophthalmology & Visual Science 51(3): 1341-1347.

Xiang, F., M. He and I. G. Morgan (2012). "Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children." Ophthalmology 119(7): 1478-1484.

Xiong, R., Z. Zhu, Y. Jiang, X. Kong, J. Zhang, W. Wang, K. Kiburg, Y. Yuan, Y. Chen, S. Zhang, M. Xuan, J. Zeng, I. G. Morgan and M. He (2022). "Sustained and rebound effect of repeated low-level red-light therapy on myopia control: A 2-year post-trial follow-up study." Clinical & Experimental Ophthalmology 50(9): 1013-1024.

Xu, R., A. Bradley and L. N. Thibos (2013). "Impact of primary spherical aberration, spatial frequency and Stiles Crawford apodization on wavefront determined refractive error: a computational study." Ophthalmic & Physiological Optics 33(4): 444-455.

Yam, J. C., Y. Jiang, S. M. Tang, A. K. P. Law, J. J. Chan, E. Wong, S. T. Ko, A. L. Young, C. C. Tham, L. J. Chen and C. P. Pang (2018). "Low-Concentration Atropine for Myopia Progression (LAMP) Study A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control." Ophthalmology 126(1): 113-124.

Yoshida, R., K. Sakai, T. Okano and Y. Sakurai (1991). "A New Model for Zero-Order Drug Release I. Hydrophobic Drug Release from Hydrophilic Polymeric Matrices." Polymer Journal 23(9): 1111-1121.

Young, G. (2024). Chapter 8 - Soft Lens Design and Fitting. Contact Lens Practice (Fourth Edition). N. Efron. New Delhi, Elsevier: 90-99.e91.

Young, G., C. P. Grey and E. B. Papas (1990). "Simultaneous vision bifocal contact lenses: a comparative assessment of the in vitro optical performance." Optometry & Vision Science 67(5): 339-345.

Zadnik, K., D. O. Mutti, G. L. Mitchell, L. A. Jones, D. Burr and M. L. Moeschberger (2004). "Normal Eye Growth in Emmetropic Schoolchildren." Optometry and Vision Science 81(11): 819-828.

Zhang, X. J., Y. Zhang, B. H. K. Yip, K. W. Kam, F. Tang, X. Ling, M. P. H. Ng, A. L. Young, P.-C. Wu, C. C. Tham, L. J. Chen, C. P. Pang and J. C. Yam (2024). "Five-Year Clinical Trial of Low-concentration Atropine for Myopia Progression (LAMP) Study: Phase 4 Report." Ophthalmology 131(9): 1011-1020.

Zheleznyak, L., A. Barbot, A. Ghosh and G. Yoon (2016). "Optical and neural anisotropy in peripheral vision." Journal of Vision 16(5): 1.