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Interventions for myopia control in children: a living systematic review and network meta-analysis (Protocol)

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[Intervention Protocol]

Interventions for myopia control in children: a living systematic review and network meta-analysis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the comparative efficacy of optical, pharmacological and environmental interventions for slowing myopia progression in children using network meta-analysis.

To generate a relative ranking of the interventions for myopia control according to their efficacy.

To produce a brief economic commentary, summarising the economic evaluations assessing interventions for myopia control in children.

To maintain the currency of the evidence using a living systematic review approach.

BACKGROUND

Description of the condition

Myopia (or nearsightedness) is a common refractive anomaly of the eye that occurs when parallel rays of light are brought to a focus in front of the retina with accommodation at rest, causing distant objects to appear blurred and near objects to remain clear (Morgan 2012). Myopia most often results from the eyeball being too long (axial elongation), but can also occur when the image-forming structures of the eye are too strong (Flitcroft 2019).

The prevalence of myopia shows significant age, ethnic and regional variation (Rudnicka 2016). Currently, 30% to 50% of adults in the USA and Europe are myopic (Dolgin 2015). Myopia is already reaching "epidemic" proportions in children and young adults in urban areas of East and South East Asia, with over 80% of children being myopic by the time they complete their high school education (Dolgin 2015). If current trends continue, it is estimated that by 2050 there will be approximately 5 billion (5000 million) people with myopia (50% of the world's population), with around 10% having high myopia (defined as a spherical equivalent of -5 dioptres (D) or worse) (Holden 2016).

The aetiology of myopia involves a complex interaction between environmental and genetic factors. Although genetic inheritance is a well-established predisposing factor for myopia, genetic factors cannot explain the rapidly rising prevalence of the condition (Williams 2019). A recent Mendelian randomisation study using the UK Biobank cohort, provided strong evidence for the cumulative effect of additional years in education on myopia development (Mountjoy 2018). Mendelian randomisation is a statistical approach that uses genetics to provide information about the relationship between an exposure and outcome. This study estimated that for each additional year in education, myopic spherical equivalent increased by -0.27 D. Evidence from a number of observational studies further supports the causal association between environmental and social factors and myopia development (Morgan 2018).

Epidemiological studies have shown that myopia is an established risk factor for a number of ocular pathologies, including cataract, glaucoma and retinal detachment (Flitcroft 2012). Although myopia-related complications can occur irrespective of age and degree of myopia (Dhakal 2018), the excessive axial elongation associated with higher degrees of myopia causes biomechanical stretching of the outer coat of the eye, increasing the risk of sight-threatening pathologies such as posterior staphyloma and myopic maculopathy (Saw 2005; Verkicharla 2015). A meta-analysis of population studies reporting blindness and visual impairment due to myopic maculopathy (Fricke 2018), estimated that in 2015, approximately 10 million people had visual impairment due to myopic macular degeneration, of whom 3 million were blind. Although the sight-threatening pathologies associated with myopia usually occur later in life, the underlying myopia develops during childhood and therefore interventions to reduce the progression of myopia have the potential to reduce future visual impairment.

Description of the intervention

Most cases of myopia develop during childhood and the prevalence of myopia begins to increase noticeably after the age of six years (McCullough 2016). Progression rates vary significantly, with rates in Asian children being approximately 0.20 D per year faster than their age-matched European counterparts (Donovan 2012). Since myopia tends to stabilise in late adolescence, interventions to slow myopia progression need to be delivered in childhood.

Interventions to slow progression of myopia can be grouped into three broad categories: optical, pharmacological and environmental (Wildsoet 2019). Optical interventions include a variety of spectacle and contact lens designs. Spectacles are the least invasive and most accessible method for potentially slowing myopia. Spectacle options include refractive under-correction, customised spectacle lenses, as well as bifocal and progressive addition designs. Soft multifocal and approved myopia control contact lenses are increasingly being used for myopia management in children (Efron 2020). Centre-distance soft multifocal lens designs incorporate a central zone that contains the distance correction with peripheral regions of the lens containing increased positive power (myopic defocus). This is achieved by either a gradual increase in power towards the periphery or using concentric peripheral zones of alternating myopic defocus and distance correction. Orthokeratology (ortho-K) involves the use of specialised rigid contact lenses that are worn during sleep to change the topography of the cornea to reduce myopic refractive error and also manipulate peripheral retinal defocus to slow eye growth. Safety remains a concern because of the risk of sight-threatening microbial keratitis and there is also the possibility of regression or rebound after discontinuation of lens wear or change to an alternative refractive intervention (VanderVeen 2019).

The most commonly used topical pharmacological intervention for myopia control is the non-selective muscarinic antagonist, atropine, which has been widely used in clinical trials in concentrations ranging from 0.01% to 1.0%. Although higher atropine concentrations have been shown to be effective in retarding myopia progression in children, the higher incidence of side effects with higher doses, including cycloplegia (inhibition of accommodation) and pupil dilation (which causes blur for near vision and photophobia) limits its long-term use. Furthermore, a rebound effect after discontinuation of therapy is more pronounced with higher concentrations of atropine (Chia 2014). More recent studies have evaluated the efficacy of lower concentrations to reduce side effects and lessen the likelihood of rebound. The results of these studies have led to a renewed interest in the clinical application of low-dose atropine (e.g. 0.01% and 0.05%) for myopia control (Wu 2019). Other pharmacological agents that have been evaluated for myopia control include tropicamide, cyclopentolate, the selective M1 muscarinic antagonist, pirenzipine, and the oral adenosine antagonist, 7-Methylxanthine.

Evidence that more time spent on near work activities is associated with higher odds of developing myopia (Huang 2015), and the observation that increased time spent outdoors is protective against myopia, after adjusting for near work, parental myopia and ethnicity (Rose 2008), have raised the possibility that environmental or behavioural interventions could be effective for myopia control. Trials of school-based programs that promote outdoor activities, conducted in East Asia, have reported a lower incidence of myopia onset but no significant effect on progression following onset of myopia (He 2015; Wu 2018).

How the intervention might work

Studies in experimental animals have shown that optically-induced changes to the effective refractive status of the eye can regulate eye growth and influence refractive development (Troilo 2019). Specifically, the observation that imposed relative myopic defocus (image focused in front of the retina) can slow axial elongation has been the impetus for the development of novel multifocal spectacles and contact lenses that provide clear central vision, whilst at the same time presenting myopic defocus over a large proportion of the visual field. The critical area ratio required for these simultaneous competing defocus signals to dominate eye growth is currently unclear. However, the relative treatment effects reported for different optical treatment regimens suggest that there appears to be an eccentricity-dependent decrease in the efficacy of myopic defocus beyond the near periphery (Smith 2014; Smith 2020).

Orthokeratology involves corneal reshaping lenses that are worn overnight to flatten the central cornea and reduce its dioptric power. The geometry of these lenses also creates a corneal profile that produces relative myopic defocus.

The precise mechanism by which anti-muscarinic agents reduce myopic progression is not fully understood. A non-accommodative mechanism is thought to be the most likely, and alternative targets have been proposed, including eye growth regulatory pathways that arise in the retina and are relayed to the sclera via the retinal pigment epithelium and choroid (McBrien 2013, Upadhyay 2020).

The protective effect of increased time outdoors on myopia development is thought to be related to the higher light intensity of sunlight and possibly its spectral composition (French 2013). Light levels have been shown to influence refractive development in animal models (Smith 2012). Higher light intensities stimulate retinal dopamine production, which is thought to inhibit axial elongation (Feldkaemper 2013).

Why it is important to do this review

As a result of its increasing global prevalence and association with sight-threatening pathologies, myopia is emerging as a major public health concern. Myopia is predicted to affect almost half of the world's population by 2050, and the pathologic consequences of high myopia increase the risk of irreversible visual impairment and blindness. There has been considerable interest in the development of strategies to delay the onset of myopia and slow its progression. Myopia control interventions are increasingly being used in routine clinical practice (Efron 2020; Wolffsohn 2016). Evidence from randomised controlled trials (RCTs) indicates that the progression of myopia can be slowed by different interventions, although treatment efficacy is highly variable.

There is a broad consensus that the primary endpoints for judging efficacy in clinical trials of myopia control interventions should include change in axial length in addition to change in refractive error (Walline 2018, Wolffsohn 2019). Myopia development and progression usually occur due to axial elongation. Therefore, axial length may be a better predictor of future progression and consequent risk of posterior pole complications (Brennan 2020). In terms of a minimally important difference of the key efficacy outcomes in myopia control trials, an expert panel concluded that a mean difference between intervention groups of 0.25 D per year would be regarded as clinically significant (0.75 D over the course of a three-year study) (Walline 2018). This would correspond to a change in axial length of approximately 0.1 mm per year.

An updated Cochrane Review, published in January 2020 (Walline 2020), evaluated the efficacy of a number of interventions, including spectacles, contact lenses and pharmaceutical agents, for slowing the progression of myopia in children. This review concluded that topical anti-muscarinic medication was effective in slowing myopia progression. Multifocal lenses, either spectacles or contact lenses, also conferred a small benefit. Although the update was published in 2020, the review only included evidence published up to the end of 2018. Consequently, in this rapidly moving field, the results of important trials have subsequently been reported.

Eye care professionals often find it difficult to assimilate potentially conflicting evidence to inform their clinical decision-making (Douglass 2020). It is therefore important that practitioners can access high-quality and up-to-date evidence to inform practice. Moreover, parents of myopic children also need reliable information to help them to understand and interpret research findings. Given the large number of different interventions available for myopia control and the large number of completed and ongoing RCTs on this topic, there is an urgent need to evaluate the comparative effectiveness of different interventions. A network meta-analysis (NMA) offers an advantage over a standard pairwise meta-analysis in that it provides both direct comparisons of individual trials and indirect comparisons not directly evaluated in trials across a network of studies, thus generating the comparativeness of all interventions in a coherent manner. A NMA can also provide relative rankings of interventions to inform clinical decision-making.

There are significant resource implications associated with myopia for both individuals and health care systems. This includes both corrected and uncorrected myopic refractive error. Lim 2009 estimated the mean direct costs of managing myopia in school-aged children in Singapore. These costs included optometrist visits, spectacles, contact lenses and travel costs. The mean cost was estimated as USD 148 (median SGD 83.33) per year in 2006. In addition, Zheng 2013 estimated the lifetime costs for a person with myopia over an 80-year lifespan to be USD 17,020 in 2011. There are also associated costs and quality of life impacts associated with uncorrected refractive error. Tahhan 2013 found a significant reduction in health state utility associated with uncorrected refractive error. Fricke 2012 estimated that the direct costs of correcting all cases of uncorrected refractive error globally would be approximately USD 28 billion (USD 28,000 million; price year not stated). Given these cost estimates, understanding the current evidence base for myopia control is key for both individuals and healthcare decision-makers.

Following publication, we plan to maintain this review as a living systematic review. This will involve searching the literature every six months and incorporating new evidence as it becomes available. This approach is appropriate for this review since it addresses an important clinical topic and there is currently significant uncertainty as to the most effective intervention. It is therefore important that consumers and healthcare providers have access to the most up-to-date evidence to make informed decisions. The review authors are aware of several relevant ongoing trials that will be important to incorporate in a timely manner.

OBJECTIVES

To assess the comparative efficacy of optical, pharmacological and environmental interventions for slowing myopia progression in children using network meta-analysis.

To generate a relative ranking of the interventions for myopia control according to their efficacy.

To produce a brief economic commentary, summarising the economic evaluations assessing interventions for myopia control in children.

To maintain the currency of the evidence using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials of optical, pharmacological and environmental interventions used alone or in combination for slowing the progression of myopia in children.

Types of participants

This review will consider studies that included children 18 years old and younger. We will exclude trials in which the majority of participants were older than 18 years at the start of the trial. We will also exclude trials that included participants with spherical equivalent myopia less than 0.50 D at baseline. The spherical equivalent is calculated by the sum of the spherical power plus half the cylindrical power of the refractive error.

We will include all participants who were randomised to the intervention comparisons of interest and had the relevant outcomes measured, irrespective of whether the outcomes were reported.

Types of interventions

We will include trials in which any of the interventions listed below were compared with a control group, or with each other. For the purposes of the analysis, we will define a control group as a placebo intervention or single vision spectacle or contact lenses.

- Undercorrection of myopia
- Bifocal or progressive addition spectacle lenses, single vision peripheral defocus spectacle lenses
- Concentric bifocal soft contact lenses, multifocal soft contact lenses, rigid gas permeable contact lenses or corneal reshaping (orthokeratology) contact lenses
- Atropine (stratified according to dosing regime as high (≥ 0.5%), moderate (0.1 % to < 0.5%) and low (< 0.1%)
- Other pharmaceutical agents (e.g. pirenzepine, 7-Methylxanthine)
- Environmental interventions (e.g. time spent outdoors, modifications to the performance of near work)

Types of outcome measures

Critical outcomes

Progression of myopia

Progression of myopia will be assessed by:

- mean change in refractive error (spherical equivalent in D) from baseline for each year of follow-up and measured by any method (e.g. objective or subjective refraction); and
- mean change in axial length for each year of follow-up in millimetres (mm) and measured by any method (e.g. ultrasound or optical biometry).

Change in refractive error and axial length following cessation of treatment

To evaluate rebound when children in the treatment group are switched to the control treatment and followed for a minimum period of one year.

Important outcomes

Incidence of adverse events

Quality of life

Measured by any validated vision-related or health-related quality of life questionnaire (e.g. National Eye Institute (NEI) Visual Function Questionnaire 25 (NEI VFQ-25), or EuroQol questionnaire, EQ-5D)

Treatment adherence

Follow-up

We will report outcomes at one year, two years and as available for the duration of the study. We will impose no restrictions based on the length of follow-up.

Brief economic commentary

We also plan to present any evidence regarding relevant economic evaluations, as a brief economic commentary.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no restrictions to language or date of publication. In addition searches will be carried out on MEDLINE and Embase using economic search filters to specifically identify economic studies and for adverse effects information relevant to this review.

This review will be developed as a living systematic review and the searches will be re-run on a six monthly basis.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) (Appendix 1).
- MEDLINE Ovid (1946 to present) (Appendix 2).
- MEDLINE Ovid - economic search (1946 to present) (Appendix 3).
- MEDLINE Ovid - adverse events (1946 to present) (Appendix 4).
- Embase Ovid (1980 to present) (Appendix 5).
- Embase Ovid - economic search (1980 to present) (Appendix 6).
- Embase Ovid - adverse events (1980 to present) (Appendix 7).

- ISRCTN registry (www.isrctn.com/editAdvancedSearch) (Appendix 8).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 9).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 10).

Searching other resources

We will search the reference lists of identified trial reports to identify additional trials. We will also contact the principal investigators of included trials for details of other potentially relevant trials not identified by the electronic searches, and of recently completed or ongoing trials.

Data collection and analysis

Selection of studies

The Information Specialist at Cochrane Eyes and Vision will download all titles and abstracts retrieved from the electronic searches to EndNote (www.endnote.com/) and remove duplicates before uploading to Covidence (Covidence). Two review authors will independently review the titles and abstracts of the search results based on the eligibility criteria stated above. Abstracts will be categorised for inclusion as 'Yes', 'Maybe' or 'No'. We will obtain the full text of articles for the studies categorised as 'Maybe' and 'Yes', and reassess them for final eligibility. After examining the full text, studies will be labelled as 'include' or 'exclude'. Studies selected as 'exclude' by both authors will be excluded from the review. We will document the reasons for exclusion. We will resolve any screening discrepancies through discussion or, if necessary, through consultation with a third author. One review author (AK) will screen the economic search results.

Living systematic review considerations

We will immediately screen any new citations retrieved by the six-monthly searches.

Data extraction and management

For eligible studies, two review authors will extract the data using a piloted data extraction form. We will contact the authors of the original reports to obtain further details if the data reported are unclear or incomplete. One review author will enter the data into Review Manager (RevManWeb) (RevMan Web 2021), and a second review author will verify that the data have been entered correctly. We will extract the following study characteristics, which may act as effect modifiers.

- Methods: study design, number and location of study centre(s), date of study and total duration.
- Participants: inclusion and exclusion criteria, number randomised, number lost to follow-up or withdrawn, number analysed, mean age and standard deviation (SD), age range, gender.
- Interventions: description of intervention and comparator.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported. Unit of analysis.
- Notes: funding for trial and conflicts of interest of trial authors.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in the included studies for all outcomes using the revised Cochrane risk of bias tool for randomised trials (RoB 2), described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (hereafter referred to as the *Cochrane Handbook;* Higgins 2019a). The risk of bias tool covers five domains of bias:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

These domain-level judgements provide the basis for an overall risk of bias judgement for the specific outcome being assessed. The response options for an overall risk of bias judgement in RoB 2 are the same as for individual domains (i.e. 'low risk of bias'; 'some concerns'; 'high risk of bias').

If applicable, we will use the versions of RoB 2 designed for cluster-randomised and cross-over trials.

We will assess the effect of assignment to intervention (the intention-to-treat effect).

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will report mean differences (MDs) for continuous outcome measures and risk ratios (RRs) for dichotomous outcomes. If different instruments are used to measure the same continuous outcome, we will use the standardised mean difference (SMD) with 95% confidence intervals (CIs).

Unit of analysis issues

When only one eye per participant is randomised, the unit of analysis will be the individual eye (participant). When both eyes from the same participant are randomised (either to the same or different interventions), we will attempt to analyse data that has been adjusted for clustering or paired-eye design. In multi-arm trials, we will treat the multiple comparisons as being independent in pairwise meta-analyses. In the NMA, we will account for the correlation between the effect sizes derived from the same study.

If we identify cluster RCTs, we will include these in meta-analyses directly where the sample size has been adjusted for clustering. We will consider it reasonable to combine the results from individual- and cluster-randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of the intervention and the unit of randomisation is considered to be unlikely. If outcomes are presented at individual level (i.e. a unit of analysis error) we will use established methods to adjust for clustering by calculating an effective sample size by dividing the original sample size by the design effect which can be calculated from the average cluster size and the intra-class correlation coefficient (ICC). Where the ICC is unknown, this will be estimated from similar trials.

For cross-over trials, estimates that properly account for the cross-over design will be handled in the same way as estimates from parallel-group trials. For inappropriately reported cross-over trials, we will attempt to approximate a paired analysis by imputing missing standard deviations as described in Chapter 23 of the *Cochrane Handbook* (Higgins 2019b).

Dealing with missing data

We will contact study authors to verify key study characteristics and obtain missing outcome data. If we do not receive a response within eight weeks, we will analyse the studies based on available data. We will use the RevMan calculator to calculate missing standard deviations using other data from the trial (e.g. confidence intervals) based on methods outlined in Chapter 10 of the *Cochrane Handbook* (Deeks 2020). We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect using sensitivity analysis.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity for each pairwise meta-analysis by comparing the characteristics of included studies and by visual inspection of forest plots. We will assess statistical heterogeneity quantitatively for direct comparisons using the Chi^2 test and the I^2 values. We will interpret I^2 values according to Chapter 9 of the *Cochrane Handbook* (McKenzie 2019), as follows:

- 0% to 40% may not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

For the NMA, we will assume a common estimate for the heterogeneity variance across the different comparisons. The assessment of statistical heterogeneity will be based on the magnitude of the heterogeneity variance parameter (Tau^2) estimated from the NMA models.

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally, we will use the node splitting approach (Dias 2010), which separates evidence for a particular comparison (node) depending on whether it comes from studies that provide 'direct' or 'indirect' information about a particular effect. We will assume a common heterogeneity estimate within each loop.

Global approaches for evaluating inconsistency

To check the assumption of consistency across the entire network, we will use the 'design by treatment' interaction model using the 'network' command in STATA (White 2015). This method accounts for different sources of inconsistency that can occur when studies with different designs are incorporated into the network (e.g. two-arm trials versus multi-arm trials), as well as inconsistency between direct and indirect evidence. We will judge the presence of inconsistency from any source in the entire network based on the Chi^2 test.

Assessment of reporting biases

We will use comparison-adjusted funnel plots to assess small study effect, which could be due to publication bias (Chaimani 2015). If there are sufficient studies, we also plan to run network meta-regression models to detect associations between study size and effect size.

Data synthesis

We will initially carry out standard pairwise meta-analyses to pool outcome data using random-effects models in RevMan Web. For comparisons with three or fewer trials, we will use a fixed-effect model. We will combine change from baseline data in meta-analyses with mean outcome data using the generic inverse variance (unstandardised) MD method, as outlined in Chapter 10 of the *Cochrane Handbook* (Deeks 2020). In the case of substantial clinical, methodological or statistical heterogeneity, we will not attempt to combine data from individual trials but will report study results separately.

If the included studies are sufficiently similar with respect to the distribution of effect modifiers, we will conduct a NMA for myopia progression as defined by change in spherical equivalent refractive error and axial length using random-effects multivariate models (Chaimani 2013; Chaimani 2015; White 2015). We will perform this analysis using the network suite of programs available in STATA (http://www.stata.com). We will assume a common heterogeneity across all comparisons in the network. For all outcomes where NMA is possible, will use the mean rank value to rank the interventions for all available outcomes (Chaimani 2015; Salanti 2012).

In our primary analysis, each pharmacological intervention will be considered as a node in the analysis regardless of the doses. In a secondary analysis, we will investigate the effect of dose of specific pharmacological interventions by splitting them into separate nodes. We do not anticipate a strong dose-response effect except for atropine. Note that atropine will be grouped according to dosing regime as high (≥ 0.5%), moderate (0.1 % to < 0.5%) and low (< 0.1%). For multifocal soft contact lenses, these will be grouped into a single node for the primary analysis and then split according to the add power (≤ +2.00 D or > +2.00 D) in a secondary analysis.

If we are unable to perform a meta-analysis, we will undertake a narrative synthesis following guidance in Chapter 12 of the *Cochrane Handbook* (McKenzie 2020). Specifically, we will present the effect estimates in structured tables and provide a descriptive summary of the range and distribution of the observed effects. In particular, we will note the direction of effects and whether these are consistent in the individual studies.

Brief economic commentary (BEC)

Following the search outlined in the Search methods for identification of studies, we will develop a BEC to summarise the availability and principal findings of the full economic evaluations assessing interventions for myopia control in children as outlined in Chapter 20 of the *Cochrane Handbook* (Aluko 2020). This BEC will encompass full economic evaluations (i.e. cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses) conducted as part of a single empirical study, such as a RCT, a model based on a single such study or a model based on several such studies.

Living systematic review considerations

Whenever we identify new evidence (i.e. new studies, data, or other information) that is relevant to the review, we will extract

the data and assess risk of bias, as appropriate. We will wait until the accumulating evidence changes one or more of the following components of the review before incorporating it and re-publishing the review.
• The findings of one or more outcomes (e.g. clinically important change in size or direction of effect).
• Credibility (e.g. change in the confidence in one or more CINeMA domains (Confidence In Network Meta-analysis; Salanti 2014)).

Formal sequential meta-analysis approaches will not be used for updated meta-analyses.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for types of intervention modalities (i.e. spectacle and contact lens designs, and specific pharmaceutical agents). If sufficient studies are available, we will also conduct subgroup analyses according to:

- participant age (< 12 years versus > 12 years);
- ethnicity (Asian versus non-Asian);
- degree of myopia at baseline; and
- administration frequency and dose of particular pharmaceutical interventions (e.g. low-, moderate- and high-dose atropine).

We will assess subgroup differences within the networks for the primary outcome by comparing their relative treatment effects and their relative treatment ranking.

Sensitivity analysis

We will undertake sensitivity analyses by removal of trials that caused high heterogeneity in direct comparisons. We will also explore the impact of including studies at high risk of bias and with high levels of missing data in the overall assessment of treatment effect.

Methods for future updates

We will review the scope and methods of this review annually in light of potential changes in the topic area or in evidence available for inclusion in the review. Each year, we will consider the necessity for the review to be a living systematic review by assessing ongoing relevance of the question to decision-makers and by determining whether uncertainty is ongoing in the evidence and whether further relevant research is likely.

Summary of findings and assessment of the certainty of the evidence

We will follow methods presented in Yepes-Nunez 2019 to prepare Summary of findings tables for the NMA.

These outcomes will be included in the Summary of findings tables:

- progression of myopia;
- change in refractive error and axial length following cessation of treatment;
- incidence of adverse events;
- quality of life; and
- treatment adherence

Evaluating confidence in the evidence

We will use the CINeMA framework for evaluating the confidence in the domains (Salanti 2014): within-study bias (i.e. risk of bias in the included studies), across-studies bias (i.e. publication and other reporting bias in the included studies), indirectness, imprecision, heterogeneity and incoherence. CINeMA assigns judgements at three levels (no concerns, some concerns, or major concerns) to each of the six domains. Judgements across the six domains are then summarised to obtain four levels of confidence for each relative treatment effect, corresponding to the usual GRADE approach: very low, low, moderate, or high (Nikolakopoulou 2020). Among the six confidence domains, the domains for within-study bias and indirectness are based on the contribution made by each study to each estimate of effect on a 0% to 100% scale ('percentage contribution matrix'). Judgement on imprecision, heterogeneity, and incoherence relies on defining relative treatment effects that exclude any clinically important differences in outcomes between interventions.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Myopia] explode all trees
#2 myop*
#3 short near sight*
#4 #1 or #2 or #3
#5 (undercorrect* or slow* or progress* or control* or retard* or funct*) near/5 (myopia or myopic or myopes)
#6 (bifocal or multifocal) near/4 (myopia or myopic) near/4 (slow* or progress* or control*)
#7 prismatic bifocal*
#8 prism near/2 bifocal*
#9 base-in prism
#10 executive near/2 bifocal*
#11 progressive next addition near/3 lens*
#12 positive next lens* near/3 addition
#13 PA-PALs
#14 peripheral near/2 defocus near/4 lens*
#15 Defocus Incorporated Multiple Segments
#16 MyoVision or MyopiLux or Myosmart
#17 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 (Concentric or gradient) near/3 lens*
#19 dual near/2 focus*
#20 extend* near/2 depth near/3 focus
#21 extend* near/2 depth near/4 field*
#22 extend* near/2 range near/3 focus
#23 extend* near/2 range near/4 field*
#24 extend* near/2 DOF
#25 EDOF
#26 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#27 #5 and #26
#28 MiSight or Biofinity Multifocal or Proclear Multifocal
#29 MeSH descriptor: [Orthokeratologic Procedures] explode all trees
#30 orthokeratology or Ortho-K
#31 #28 or #29 or #30
#32 MeSH descriptor: [Atropine] explode all trees
#33 atropine*
#34 MeSH descriptor: [Cyclopentolate] explode all trees
#35 cyclopentolate*
#36 MeSH descriptor: [Pirenzepine] explode all trees
#37 pirenzepine*
#38 MeSH descriptor: [Tropicamide] explode all trees
#39 tropicamide*
#40 methylxanthine*
#41 #5 #32 or #33 or #34 or #35 #36 or #37 or #38 or #39 or #40
#42 MeSH descriptor: [Leisure Activities] explode all trees
#43 outdoor* or out door*
#44 outside or out side
#45 #42 or #43 or #44
#46 #5 or #17 or #27 or #31 or #41 or #45
#47 MeSH descriptor: [Child] explode all trees
#48 MeSH descriptor: [Adolescent] this term only
#49 MeSH descriptor: [Pediatrics] explode all trees
#50 boy* or girl* or child* or minor*
#51 adolescen* or juvenile* or teen or teens or teenage* or youth or youths or underage
#52 (primary or elementary or high or secondary) near/1 school*
#53 paediatric* or pediatric*
#54 #47 or #48 or #49 or #50 or #51 or #52 or #53
#55 #4 and #46
#56 #54 and #55

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp myopia/
14. (myopia or myopic or myopes).tw.
15. ((short or near) adj3 sight$).tw.
16. or/13-15
17. ((undercorrect$ or slow$ or progress$ or control$ or retard$ or funct$) adj5 (myopia or myopic or myopes)).tw.
18. ((bifocal or multifocal) adj4 (myopia or myopic) adj4 (slow$ or progress$ or control$)).tw.
19. prismatic bifocal$.tw.
20. (near adj1 prism adj4 bifocal$).tw.
21. base-in prism.tw.
22. (executive adj2 bifocal$).tw.
23. (progressive adj1 addition adj3 lens$).tw.
24. (positive adj1 lens$ adj3 addition).tw.
25. PA-PALs.tw.
26. (peripheral adj2 defocus adj4 lens$).tw.
27. Defocus Incorporated Multiple Segments.tw.
28. (MyoVision or MyopiLux or Myosmart).tw.
29. or/18-28
30. ((Concentric or gradient) adj3 lens$).tw.
31. (dual adj2 focus$).tw.
32. (extend$ adj2 depth adj3 focus).tw.
33. (extend$ adj2 depth adj4 field$).tw.
34. (extend$ adj2 range adj3 focus).tw.
35. (extend$ adj2 range adj4 field$).tw.
36. (extend$ adj2 DOF).tw.
37. EDOF.tw.
38. or/30-37
39. 17 and 38
40. (MiSight or Biofinity Multifocal or Proclear Multifocal).tw.
41. Orthokeratologic Procedures/
42. (orthokeratology or Ortho-K).tw.
43. or/40-42
44. Atropine/
45. atropine$.tw.
46. Cyclopentolate/
47. cyclopentolate$.tw.
48. Pirenzepine/
49. pirenzepine$.tw.
50. Tropicamide/
51. tropicamide$.tw.
52. methylxanthine$.tw.
53. or/44-52
54. exp Leisure Activities/
55. (outdoor$ or out door$).tw.
56. (outside or out side).tw.
57. (near adj2 work$).tw.
58. or/54-57
59. 17 or 29 or 39 or 43 or 53 or 58
60. exp Child/

61. Adolescent/
62. exp Pediatrics/
63. (boy$ or girl$ or child$ or minor$).tw.
64. (adolescen$ or juvenile$ or teen or teens or teenage$ or youth or youths or underage).tw.
65. ((primary or elementary or high or secondary) adj1 school$).tw.
66. (schoolchild$ or schoolage or schoolboy$ orschoolgirl$ or highschool$).tw.
67. (paediatric$ or pediatric$).tw.
68. or/60-67
69. 16 and 59
70. 12 and 69
71. 68 and 70

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. MEDLINE Ovid economics search strategy

1. Economics/
2. exp "costs and cost analysis"/
3. Economics, Dental/
4. exp economics, hospital/
5. Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. value for money.ti,ab.
11. budget$.ti,ab.
12. or/1-11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13-15
17. 12 not 16
18. letter.pt.
19. editorial.pt.
20. historical article.pt.
21. or/18-20
22. 17 not 21
23. exp animals/ not humans/
24. 22 not 23
25. bmj.jn.
26. "cochrane database of systematic reviews".jn.
27. health technology assessment winchester england.jn.
28. or/25-27
29. exp myopia/
30. (myopia or myopic or myopes).tw.
31. ((short or near) adj3 sight$).tw.
32. or/29-31
33. ((undercorrect$ or slow$ or progress$ or control$ or retard$ or funct$) adj5 (myopia or myopic or myopes)).tw.
34. ((bifocal or multifocal) adj4 (myopia or myopic) adj4 (slow$ or progress$ or control$)).tw.
35. prismatic bifocal$.tw.
36. (near adj1 prism adj4 bifocal$).tw.
37. base-in prism.tw.
38. (executive adj2 bifocal$).tw.
39. (progressive adj1 addition adj3 lens$).tw.
40. (positive adj1 lens$ adj3 addition).tw.
41. PA-PALs.tw.
42. (peripheral adj2 defocus adj4 lens$).tw.
43. Defocus Incorporated Multiple Segments.tw.
44. (MyoVision or MyopiLux or Myosmart).tw.
45. or/34-44
46. ((Concentric or gradient) adj3 lens$).tw.

47. (dual adj2 focus$).tw.
48. (extend$ adj2 depth adj3 focus).tw.
49. (extend$ adj2 depth adj4 field$).tw.
50. (extend$ adj2 range adj3 focus).tw.
51. (extend$ adj2 range adj4 field$).tw.
52. (extend$ adj2 DOF).tw.
53. EDOF.tw.
54. or/46-53
55. 33 and 54
56. (MiSight or Biofinity Multifocal or Proclear Multifocal).tw.
57. Orthokeratologic Procedures/
58. (orthokeratology or Ortho-K).tw.
59. or/56-58
60. Atropine/
61. atropine$.tw.
62. Cyclopentolate/
63. cyclopentolate$.tw.
64. Pirenzepine/
65. pirenzepine$.tw.
66. Tropicamide/
67. tropicamide$.tw.
68. methylxanthine$.tw.
69. or/60-68
70. exp Leisure Activities/
71. (outdoor$ or out door$).tw.
72. (outside or out side).tw.
73. (near adj2 work$).tw.
74. or/70-73
75. 33 or 45 or 55 or 59 or 69 or 74
76. 32 and 75
77. 28 and 76

Appendix 4. MEDLINE Ovid adverse events search strategy

1. (ae or co or de).fs.
2. (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ti,ab.
3. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
4. or/1-3
5. exp myopia/
6. (myopia or myopic or myopes).tw.
7. ((short or near) adj3 sight$).tw.
8. or/5-7
9. ((undercorrect$ or slow$ or progress$ or control$ or retard$ or funct$) adj5 (myopia or myopic or myopes)).tw.
10. ((bifocal or multifocal) adj4 (myopia or myopic) adj4 (slow$ or progress$ or control$)).tw.
11. prismatic bifocal$.tw.
12. (near adj1 prism adj4 bifocal$).tw.
13. base-in prism.tw.
14. (executive adj2 bifocal$).tw.
15. (progressive adj1 addition adj3 lens$).tw.
16. (positive adj1 lens$ adj3 addition).tw.
17. PA-PALs.tw.
18. (peripheral adj2 defocus adj4 lens$).tw.
19. Defocus Incorporated Multiple Segments.tw.
20. (MyoVision or MyopiLux or Myosmart).tw.
21. or/10-20
22. ((Concentric or gradient) adj3 lens$).tw.
23. (dual adj2 focus$).tw.
24. (extend$ adj2 depth adj3 focus).tw.
25. (extend$ adj2 depth adj4 field$).tw.
26. (extend$ adj2 range adj3 focus).tw.
27. (extend$ adj2 range adj4 field$).tw.
28. (extend$ adj2 DOF).tw.

29. EDOF.tw.
30. or/22-29
31. 9 and 30
32. (MiSight or Biofinity Multifocal or Proclear Multifocal).tw.
33. Orthokeratologic Procedures/
34. (orthokeratology or Ortho-K).tw.
35. or/32-34
36. Atropine/
37. atropine$.tw.
38. Cyclopentolate/
39. cyclopentolate$.tw.
40. Pirenzepine/
41. pirenzepine$.tw.
42. Tropicamide/
43. tropicamide$.tw.
44. methylxanthine$.tw.
45. or/36-44
46. exp Leisure Activities/
47. (outdoor$ or out door$).tw.
48. (outside or out side).tw.
49. (near adj2 work$).tw.
50. or/46-49
51. 9 or 21 or 31 or 35 or 45 or 50
52. 8 and 51
53. 4 and 52

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Golder 2006

Appendix 5. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31

33. myopia/
34. (myopia or myopic or myopes).tw.
35. ((short or near) adj3 sight$).tw.
36. or/33-35
37. ((undercorrect$ or slow$ or progress$ or control$ or retard$ or funct$) adj5 (myopia or myopic or myopes)).tw.
38. ((bifocal or multifocal) adj4 (myopia or myopic) adj4 (slow$ or progress$ or control$)).tw.
39. prismatic bifocal$.tw.
40. (near adj1 prism adj4 bifocal$).tw.
41. base-in prism.tw.
42. (executive adj2 bifocal$).tw.
43. (progressive adj1 addition adj3 lens$).tw.
44. (positive adj1 lens$ adj3 addition).tw.
45. PA-PALs.tw.
46. (peripheral adj2 defocus adj4 lens$).tw.
47. Defocus Incorporated Multiple Segments.tw.
48. (MyoVision or MyopiLux or Myosmart).tw.
49. or/38-48
50. ((Concentric or gradient) adj3 lens$).tw.
51. (dual adj2 focus$).tw.
52. (extend$ adj2 depth adj3 focus).tw.
53. (extend$ adj2 depth adj4 field$).tw.
54. (extend$ adj2 range adj3 focus).tw.
55. (extend$ adj2 range adj4 field$).tw.
56. (extend$ adj2 DOF).tw.
57. EDOF.tw.
58. or/50-57
59. 37 and 58
60. (MiSight or Biofinity Multifocal or Proclear Multifocal).tw.
61. orthokeratology lens/
62. (orthokeratology or Ortho-K).tw.
63. or/60-62
64. atropine/
65. atropine$.tw.
66. cyclopentolate/
67. cyclopentolate$.tw.
68. pirenzepine/
69. pirenzepine$.tw.
70. tropicamide/
71. tropicamide$.tw.
72. methylxanthine/
73. methylxanthine.tw.
74. or/64-73
75. exp recreation/
76. (outdoor$ or out door$).tw.
77. (outside or out side).tw.
78. (near adj2 work$).tw.
79. or/75-78
80. exp child/
81. exp adolescent/
82. exp pediatrics/
83. (boy$ or girl$ or child$ or minor$).tw.
84. (adolescen$ or juvenile$ or teen or teens or teenage$ or youth or youths or underage).tw.
85. ((primary or elementary or high or secondary) adj1 school$).tw.
86. (schoolchild$ or schoolage or schoolboy$ orschoolgirl$ or highschool$).tw.
87. (paediatric$ or pediatric$).tw.
88. or/80-87
89. 37 or 49 or 59 or 63 or 74 or 79
90. 36 and 89
91. 32 and 90
92. 88 and 91

Appendix 6. Embase Ovid economics search strategy

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. pharmacoeconomics/
5. or/1-4
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$ not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. or/6-9
11. 5 or 10
12. letter.pt.
13. editorial.pt.
14. note.pt.
15. or/12-14
16. 11 not 15
17. (metabolic adj cost).ti,ab.
18. ((energy or oxygen) adj cost).ti,ab.
19. ((energy or oxygen) adj expenditure).ti,ab.
20. or/17-19
21. 16 not 20
22. animal/
23. exp animal experiment/
24. nonhuman/
25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
26. or/22-25
27. exp human/
28. human experiment/
29. or/27-28
30. 26 not (26 and 29)
31. 21 not 30
32. 0959-8146.is.
33. (1469-493X or 1366-5278).is.
34. 1756-1833.en.
35. or/32-34
36. 31 not 35
37. Conference abstract.pt.
38. 36 not 37
39. myopia/
40. (myopia or myopic or myopes).tw.
41. ((short or near) adj3 sight$).tw.
42. or/39-41
43. ((undercorrect$ or slow$ or progress$ or control$ or retard$ or funct$) adj5 (myopia or myopic or myopes)).tw.
44. ((bifocal or multifocal) adj4 (myopia or myopic) adj4 (slow$ or progress$ or control$)).tw.
45. prismatic bifocal$.tw.
46. (near adj1 prism adj4 bifocal$).tw.
47. base-in prism.tw.
48. (executive adj2 bifocal$).tw.
49. (progressive adj1 addition adj3 lens$).tw.
50. (positive adj1 lens$ adj3 addition).tw.
51. PA-PALs.tw.
52. (peripheral adj2 defocus adj4 lens$).tw.
53. Defocus Incorporated Multiple Segments.tw.
54. (MyoVision or MyopiLux or Myosmart).tw.
55. or/44-54
56. ((Concentric or gradient) adj3 lens$).tw.
57. (dual adj2 focus$).tw.
58. (extend$ adj2 depth adj3 focus).tw.
59. (extend$ adj2 depth adj4 field$).tw.
60. (extend$ adj2 range adj3 focus).tw.

61. (extend$ adj2 range adj4 field$).tw.
62. (extend$ adj2 DOF).tw.
63. EDOF.tw.
64. or/56-63
65. 43 and 64
66. (MiSight or Biofinity Multifocal or Proclear Multifocal).tw.
67. orthokeratology lens/
68. (orthokeratology or Ortho-K).tw.
69. or/66-68
70. atropine/
71. atropine$.tw.
72. cyclopentolate/
73. cyclopentolate$.tw.
74. pirenzepine/
75. pirenzepine$.tw.
76. tropicamide/
77. tropicamide$.tw.
78. methylxanthine/
79. methylxanthine.tw.
80. or/70-79
81. exp recreation/
82. (outdoor$ or out door$).tw.
83. (outside or out side).tw.
84. (near adj2 work$).tw.
85. or/81-84
86. 43 or 55 or 65 or 69 or 80 or 85
87. 42 and 86
88. 38 and 87

Appendix 7. Embase Ovid adverse events search strategy

1. DRUG/ae
2. (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ti,ab.
3. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
4. or/1-3
5. myopia/
6. (myopia or myopic or myopes).tw.
7. ((short or near) adj3 sight$).tw.
8. or/5-7
9. ((undercorrect$ or slow$ or progress$ or control$ or retard$ or funct$) adj5 (myopia or myopic or myopes)).tw.
10. ((bifocal or multifocal) adj4 (myopia or myopic) adj4 (slow$ or progress$ or control$)).tw.
11. prismatic bifocal$.tw.
12. (near adj1 prism adj4 bifocal$).tw.
13. base-in prism.tw.
14. (executive adj2 bifocal$).tw.
15. (progressive adj1 addition adj3 lens$).tw.
16. (positive adj1 lens$ adj3 addition).tw.
17. PA-PALs.tw.
18. (peripheral adj2 defocus adj4 lens$).tw.
19. Defocus Incorporated Multiple Segments.tw.
20. (MyoVision or MyopiLux or Myosmart).tw.
21. or/10-20
22. ((Concentric or gradient) adj3 lens$).tw.
23. (dual adj2 focus$).tw.
24. (extend$ adj2 depth adj3 focus).tw.
25. (extend$ adj2 depth adj4 field$).tw.
26. (extend$ adj2 range adj3 focus).tw.
27. (extend$ adj2 range adj4 field$).tw.
28. (extend$ adj2 DOF).tw.
29. EDOF.tw.
30. or/22-29
31. 9 and 30

32. (MiSight or Biofinity Multifocal or Proclear Multifocal).tw.
33. orthokeratology lens/
34. (orthokeratology or Ortho-K).tw.
35. or/32-34
36. atropine/
37. atropine$.tw.
38. cyclopentolate/
39. cyclopentolate$.tw.
40. pirenzepine/
41. pirenzepine$.tw.
42. tropicamide/
43. tropicamide$.tw.
44. methylxanthine/
45. methylxanthine.tw.
46. or/36-45
47. exp recreation/
48. (outdoor$ or out door$).tw.
49. (outside or out side).tw.
50. (near adj2 work$).tw.
51. or/47-50
52. 9 or 21 or 31 or 35 or 46 or 51
53. 8 and 52
54. 4 and 53

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Golder 2006.

Appendix 8. ISRCTN search strategy

myopia AND (undercorrect OR slow OR progress OR control)

Appendix 9. ClinicalTrials.gov search strategy

myopia AND (undercorrect OR slow OR progress OR control) | Interventional Studies | Child

Appendix 10. WHO ICTRP search strategy

myopia AND undercorrect OR myopia AND slow OR myopia AND progress OR myopia AND control

HISTORY

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CONTRIBUTIONS OF AUTHORS

John Lawrenson conceived the review. All authors contributed to writing the protocol.

DECLARATIONS OF INTEREST

JL: Received grant income from the National Institute for Health Research (NIHR), International Glaucoma Association (IGA) and the College of Optometrists for projects outside the submitted review.
RD: None known
PV: None known
RS: None known
BH: Is working on design optimisation of an orthokeratology lens by No7 Contact Lenses.
LD: In the past 36 months, has received funding to undertake clinical studies on contact lenses, being unrelated to this work, from Coopervision Pty Ltd. She has received consultancy funding from Medmont Pty Ltd for work relating to ophthalmic imaging devices. These consultancies do not have any relevance to the submitted work. She has received an honorarium from Optometry Australia (2020) to present a lecture on myopia management.
AK: None known
TL: None known
GV: None known
JW: Received research funding (Principal Investigator on a National Eye Institute-supported grant examining the myopia control effect of soft multifocal contact lens) and materials (Bausch + Lomb have provided contact lens solutions for his federally funded, investigator-driven study) related to myopia and/or myopia progression.

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