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Comparative Efficacy, Additivity, and Dose–Response of Myopia-Control Interventions: A Systematic Review and Network Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 September 2026 and was last updated on 14 September 2026.

INTRODUCTION

Review question / Objective Mong children and adolescents with myopia, what are the comparative effects of pharmacologic, optical, light-based, and combination myopia-control interventions on axial elongation, refractive progression, and treatment-related harms?

The primary objective is to compare the efficacy of eligible myopia-control intervention packages using a systematic review and random-effects network meta-analysis of randomized controlled trials, with change in axial length at approximately 12 months as the primary outcome.

Secondary objectives are to:

compare effects on cycloplegic spherical equivalent refraction;
examine whether combination interventions can be adequately described by additive component effects or whether evidence supports departures from additivity;
estimate component-specific effects using component network meta-analysis where model assumptions and evidence structure permit;
characterize dose–response relationships, particularly for interventions available at multiple treatment intensities or concentrations, when the prespecified evidence threshold is satisfied;
evaluate heterogeneity, inconsistency, transitivity, small-study effects, evidence fragility, and the amount of direct versus indirect evidence underlying network estimates; and
synthesize treatment-related adverse events and discontinuation where the evidence permits.

The principal clinical question is therefore not only which intervention package is most effective, but also what randomized evidence establishes about the incremental benefit of combination treatment and whether observed combination effects depart meaningfully from additivity.

Condition being studied Myopia in children and adolescents.

Myopia is a refractive condition in which parallel light rays are focused in front of the retina when accommodation is relaxed, resulting in impaired distance vision. Progression during childhood is commonly accompanied by excessive axial elongation of the eye. Greater axial length and higher degrees of myopia are associated with increased lifetime risks of retinal detachment, myopic maculopathy, glaucoma, and other vision-threatening complications.

Interventions designed to slow childhood myopia progression include atropine at different concentrations, spectacle lens designs, multifocal or myopia-control contact lenses, orthokeratology, light-based interventions, and concurrent combination strategies.

The principal disease-modification outcome in this review is axial elongation, with cycloplegic refractive progression and treatment-related harms evaluated as additional clinically important outcomes.

METHODS

Participant or population Children or adolescents with established myopia who participated in randomized controlled trials of interventions intended to slow myopia progression will be eligible.Trials enrolling mixed populations will be included only when data for the eligible myopic population can be separated or when the study population otherwise satisfies the protocol-defined eligibility criteria.Baseline characteristics relevant to effect modification and transitivity, including age, baseline refractive error, baseline axial length, recruitment region, previous myopia-control treatment, and other clinically relevant characteristics, will be extracted where reported.Studies evaluating prevention of incident myopia in non-myopic populations are outside the primary treatment network.

Intervention Eligible interventions include pharmacologic, optical, light-based, and combination strategies intended to slow progression of established myopia.These may include atropine at different concentrations; orthokeratology; myopia-control spectacle lenses; multifocal, dual-focus, or other myopia-control contact lenses; repeated low-level red-light therapy; and concurrent combinations of eligible interventions.Different clinically meaningful doses, concentrations, technologies, or treatment packages will be coded according to a prespecified intervention taxonomy.Sequential regimens will not be interpreted as concurrent combinations in the component model.

Comparator Eligible comparators include placebo, sham treatment, single-vision spectacles or other inactive/usual-care controls, another active myopia-control intervention, another dose or concentration of the same intervention, or an eligible combination/background-treatment strategy.Active-controlled, add-on, factorial, and multi-arm randomized comparisons may contribute according to their randomization structure.Eligible comparators include placebo, sham treatment, single-vision spectacles or other inactive/usual-care controls, another active myopia-control intervention, another dose or concentration of the same intervention, or an eligible combination/background-treatment strategy.Active-controlled, add-on, factorial, and multi-arm randomized comparisons may contribute according to their randomization structure.

Study designs to be included Randomized controlled trials, including parallel-group, multi-arm, factorial, randomized add-on, and eligible cluster-randomized designs. Non-randomized comparisons will not contribute to the primary efficacy network. Randomization structure will be verified from primary reports before inclusion in the definitive network analysis.

Eligibility criteria Studies will be eligible when they:use a randomized allocation design;enroll children or adolescents with established myopia;evaluate an intervention intended to slow myopia progression;compare at least two eligible intervention or control strategies;report sufficient data for at least one eligible outcome at a protocol-defined follow-up interval; andprovide sufficient information to identify and code the intervention node.The primary efficacy network will include randomized comparisons only. Non-randomized observational comparisons will not be entered into that network.Interventions will be classified according to a version-controlled taxonomy. Arms that cannot be reliably coded from the primary report will not be forced into a network node. Trials whose eligible arms collapse to the same treatment node after coding will not contribute a comparative effect to that network and will be reported descriptively where appropriate.Concurrent combination treatments may enter both the conventional package-level network and, where assumptions are satisfied, the component network. Sequential treatment schedules will be treated as intervention packages rather than concurrent component combinations.For cycloplegic spherical equivalent

analyses, refractive measurements must satisfy the protocol-defined measurement criteria. Orthokeratology-related refraction data will be admitted only when the timing, cycloplegia, treatment cessation/recovery, and other protocol-defined requirements make the measurement interpretable; where recovery remains uncertain, the comparison will be withheld from the refractive synthesis.Multiple publications from the same randomized cohort will be linked and treated as one study family. Duplicate reporting will not generate duplicated participants.Studies evaluating prevention of incident myopia rather than treatment of established myopia will be outside the primary scope.No study or treatment arm will be excluded from a sensitivity analysis solely because of the magnitude or direction of its observed treatment outcome.

Information sources Electronic bibliographic databases will include MEDLINE/PubMed, Embase, CENTRAL, and Web of Science.

Additional sources will include:

reference lists of included trials;
reference lists of relevant systematic reviews and meta-analyses;
forward citation searching;
trial registries where relevant;
hand-searching of prespecified ophthalmology journals;
related reports from identified study families; and
contact with study authors when required information, particularly dispersion measures or details necessary to determine eligibility, cannot be obtained from published reports.

Primary reports will be checked when automated or secondary-source extraction suggests that an outcome, covariate, randomization feature, or design characteristic is absent. A finding of “not reported” or “not estimable” will not be based solely on an automated text-extraction process or on absence from previous systematic reviews.

Main outcome(s) The sole primary outcome is change in axial length, measured in millimetres, at approximately 12 months according to the protocol-defined follow-up window.

The primary effect measure will be the mean difference (MD) in axial-length change between randomized treatment groups, with lower axial elongation representing greater treatment efficacy.

The principal synthesis will be a random-effects, package-level network meta-analysis. Estimates will be reported with 95% confidence intervals and, where estimable, prediction intervals.

Direct, indirect, and network evidence will be distinguished where relevant. Treatment rankings may be summarized but will not be interpreted as an unconditional hierarchy of clinical preference.

Component effects and departures from additivity will be considered secondary model-based inferences rather than substitutes for the primary treatment-package estimates.

Additional outcome(s) The key secondary efficacy outcome is change in cycloplegic spherical equivalent refraction (SER), expressed in dioptres, at approximately 12 months.

Additional outcomes include:

axial length and cycloplegic SER at longer protocol-defined landmarks where sufficient evidence exists;
treatment discontinuation and adherence;
adverse ocular or visual events, including treatment-specific events reported by randomized trials;
retinal or OCT abnormalities, afterimages, scotomata, visual-acuity loss, and other relevant adverse events where applicable;
evidence concerning persistence or rebound after cessation where a valid randomized design exists; and
dose–response relationships when prespecified evidence requirements are fulfilled.

Harms will be synthesized using odds ratios for comparative analyses when appropriate. Single-arm event incidence, when informative, will be modelled separately and will not be confused with comparative network effects.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, using the appropriate version or extension for the trial design where required.

Two reviewers will independently evaluate the relevant domains and reach a final judgment through reconciliation, with adjudication if required.

Risk-of-bias judgments will be maintained at the appropriate outcome/result level rather than treated solely as a study-wide characteristic.

For network estimates, confidence in evidence will additionally be considered using the CINeMA

framework, incorporating within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence as applicable.

Component-specific certainty considerations will be clearly labelled as a separate sensitivity framework and will not be presented as though they were standard CINeMA assessments.

Strategy of data synthesis The primary analysis will be a random-effects treatment-package network meta-analysis comparing eligible myopia-control interventions. Separate networks will be constructed for axial length and cycloplegic spherical equivalent where appropriate.

The principal efficacy scale will be the mean difference. Multi-arm randomized trials will be analysed using covariance structures that preserve correlations between non-redundant within-study contrasts.

Network synthesis will be undertaken only where clinical and methodological transitivity is defensible. If transitivity cannot reasonably be supported for a proposed network, prespecified alternatives include a restricted network, pairwise meta-analysis, or descriptive synthesis.

Heterogeneity, inconsistency, prediction intervals, the amount of direct evidence, and small-study effects will be evaluated where estimable.

A component network meta-analysis (cNMA) will be performed as a secondary analysis when the intervention network and component structure support it. The additive model will estimate effects of individual components. Potential interaction terms will be examined separately and their evidence classified according to whether they arise from factorial-direct randomized evidence, randomized add-on evidence, or indirect network identification. Failure to detect a statistically significant interaction will not be interpreted as proof of additivity.

Dose–response analyses will be undertaken only when the prespecified evidence gate is met. Candidate functional forms will be compared using the model-based dose–response framework specified in the statistical analysis plan, and only converged models meeting prespecified diagnostics will be interpreted.

Treatment rankings, contribution measures, evidence-fragility analyses, and network meta-regression will be considered supportive analyses rather than substitutes for treatment-effect estimates and uncertainty intervals.

Harms will be synthesized separately from efficacy using comparative odds-ratio models where sufficient evidence exists.

Subgroup analysis Subgroup and network meta-regression analyses will be performed only when the evidence base provides sufficient information to support interpretable comparisons.

Potential effect modifiers include:

participant age;
baseline refractive error;
baseline axial length;
East Asian versus non-East Asian recruitment setting;
publication year/study era;
previous myopia-control treatment;
intervention dose, concentration, or treatment intensity where clinically appropriate; and
characteristics relevant to add-on or combination therapy.

Distributions of potential effect modifiers across treatment comparisons will first be examined as part of the transitivity assessment.

Subgroup findings based on sparse aggregate data will be considered exploratory and will not be interpreted as individual-level treatment-effect modification.

If a prespecified subgroup cannot be estimated because the required variable is inadequately reported or there are too few informative comparisons, it will be reported as not estimable rather than replaced by a post hoc subgroup definition.

Sensitivity analysis Planned sensitivity analyses will examine the robustness of conclusions to assumptions regarding:

intervention taxonomy and clinically reasonable node grouping;
exclusion of studies with important eligibility or verification concerns;
randomized sample-size restrictions where specified;
cluster-design corrections and alternative intraclass correlation coefficients;
heterogeneity assumptions and component-model heterogeneity handling;

removal of extreme/high-dose observations in dose–response analyses; publication era/ contemporary-study restriction;
assumed correlations required for eligible multivariate analyses;
alternative specifications for exploratory ratio-scale analyses;
sparse-event methods for harms;
small-study-effect adjustments; and
alternative clinically justified model specifications.

No sensitivity analysis will exclude a trial or arm merely because its observed outcome is unusually favourable or unfavourable.

The conventional package-level NMA will remain the principal reference analysis. Results from component, dose–response, meta-regression, fragility, or other sensitivity models will be clearly distinguished from the primary analysis.

Country(ies) involved Taiwan.

Keywords myopia; myopia control; axial length; atropine; orthokeratology; optical intervention; combination therapy; network meta-analysis; component network meta-analysis; dose-response.

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