

CLINICAL SUMMARY

IMI Clinical Myopia Control Trials and Instrumentation Report

Monica Jong, PhD BOptom

Executive Director IMI

**Brien Holden Vision Institute Sydney, Visiting Fellow School of Optometry and Vision Science,
University of New South Wales, Sydney, Australia.**

James S. Wolffsohn, FCOptom PhD

IMI Committee Chair

Ophthalmic Research Group, Aston University, Birmingham, UK

INTRODUCTION

This report details evidence-based recommendations to guide clinical trial protocols and to inform future instrumentation development, facilitating the improvement and allowing for data comparison across clinical trials. The outcomes were classified as primary (refractive error and/or axial length), secondary (patient reported outcomes and treatment compliance), and exploratory (peripheral refraction, accommodative changes, ocular alignment, pupil size, outdoor activity/lighting levels, anterior and posterior segment imaging, and tissue biomechanics).

KEY FINDINGS

- I. **STUDY DESIGN:** To determine the efficacy of any treatment option/trial, a sound methodology is critical to minimize variability and bias and maximize the ability to allow for comparison with other studies. All clinical trial protocols should adhere to the tenets of the Declaration of Helsinki and be approved by the appropriate local ethics committee; informed consent should be obtained from both guardians and children; and with adverse event reporting embedded. Clinical trials should be registered on a clinical trial registry.
 - a. **Study length:** A minimum study length of three years is recommended. Trials should evaluate efficacy over a long period beyond any initial treatment effect while balancing other issues such as participant retention and costs.
 - b. **Participants Selection criteria:** Recommendations were based on 24 recent evidence-based papers from four designated categories of clinical trials: **Category 1** included multifocal spectacles and undercorrection with single vision spectacles; **Category 2** included orthokeratology (OK) lenses; **Category 3** included bifocal contact lenses and multifocal contact lenses; **Category 4** included atropine treatment. *Studies on outdoor activities were not included because the cohorts were substantially different from those in the other four categories.*
 - i. **Refractive error**
 1. Cyclopleged spherical or spherical equivalent of myopia of at least -0.75 D with astigmatism ≤ 1.00 D and anisometropia ≤ 1.50 D.
 2. Progression can be considered but difficult to assess with often minimal retrospective data

- ii. **Age:** Most studies adopted a minimum age of 6 years of age with a maximum of 12 years of age.
 - iii. **Exclusion Criteria:** Participants were excluded if they had **previous myopia control treatment**, ocular pathology, binocular vision anomalies such as strabismus, on medications that may affect pupil size, accommodation, or impact the ocular surface (such as allergy medications) and systemic disease that may affect vision, vision development, or contact lens wear (such as diabetes and Down syndrome). Consideration of previous optical correction is important.
- c. **Appropriate control (untreated) group:** A placebo-controlled clinical trial in which participants do not know their group assignment is generally considered the gold standard. The most appropriate control group will depend on the intervention being studied, and **randomized double masking** (investigator and participant unaware of the groups) should be used wherever possible to minimize the potential for bias. A concurrent control group is required to distinguish the naturally declining myopia progression and seasonal progression changes from the treatment effect. Treatment and control groups ideally should be matched for factors such as age, starting refractive error, time outdoors, ethnicity and parental myopia status since these factors are all known to influence progression rate.
- i. **Pharmaceutical studies:** The recommended placebo is the vehicle used in the active treatment intervention **without** the active pharmaceutical agent being evaluated in the treatment group.
 - ii. **Contact lens and OK studies:** The best choice for a control group depends on the lenses being evaluated. For example the control group in a soft contact lens study ideally should be wearing a contact lens made of the same material and the optics should not change peripheral defocus. OK treatment trials are impossible to double mask and single vision spectacle lenses have previously been used as the control group.
 - iii. **Multifocal Spectacle Studies:** Control groups generally used single-vision spectacle lenses. It is not possible to mask bifocal spectacle lenses.
- d. **Randomization and stratification:** Randomization is a critical part of a clinical trial that distributes potential confounding baseline characteristics (both known and unknown) between the treatment groups and the control. Randomization should be assigned **after** the investigator has confirmed the participant's eligibility to be enrolled in the clinical trial, and administered using an online portal that requires key eligibility checks prior to revealing the randomization assignment. Stratifying randomization by key factors known to influence myopia progression, such as age and ethnicity, should be considered. An **intent-to-treat philosophy** should be used when analysing data.
- e. **Masking:** Double masking should be adopted wherever possible.
- f. **Cycloplegia:** Cycloplegic refraction should be used when measuring primary outcomes in studies of myopia progression for improved accuracy. The recommended regimen in clinical trials is two drops of 1% tropicamide separated by five minutes with primary outcome measures commencing 30 minutes after the first drop of tropicamide was instilled (however ethnicity/iris color should be considered).
- g. **Assessment of rebound:** Acceleration of eye growth after cessation of the treatment is termed "**rebound**". Studies designed to evaluate potential rebound should have a minimum 1 year follow-up after stopping treatment, where all participants are switched to the control treatment, but ethical implications should be considered.

h. **Safety.**

- i. **Standardized Adverse Event Reporting:** An **adverse event** is “any untoward medical occurrence in a patient or clinical investigation participant” administered a drug or device, which “does not have to have a causal relationship” and can be any unfavorable and unintended sign, symptom or disease associated with the use of a medical device or drug. Reporting of adverse events should occur in a standardized manner and timeframe to the designated bodies.
 - ii. **Ocular Health:** At the baseline visit of each trial a detailed anterior and posterior segment including a binocular vision assessment needs to be performed. At each follow-up visit fundus evaluation is useful to detect the peripheral retinal changes.
 - iii. **Vision:** LogMAR **visual acuity** should be used for assessing safety and to assess any impact of optical, pharmaceutical, or environmental modifications both during and after treatment. Reading speed may be useful as it has been found to correlate better with vision related quality of life (satisfaction with **functional vision**) than does high contrast visual acuity.
 - iv. **Dysphotopsia:** Dysphotopsia, such as glare, is of interest in myopia control strategies that affect light levels, alter the light spectrum entering the eye, dilate the pupil, or impose optical junctions (such as different or alternating power SCL optical zones) within the pupil.
- i. **Clinically meaningful effect:** Defining and reporting a clinically meaningful effect is important in the clinical outcome studies. The mean and standard deviation of the difference in progression between groups, as well as a thorough description of the groups and any matching P values, and 95% confidence interval values should also be reported. If reporting percent reduction in myopia progression, the duration of treatment, sample population, and study design should also be included. Other ways to report efficacy are further detailed in the full report.

II. CLINICAL TRIAL OUTCOMES AND RELATED INSTRUMENTATION

a. **Primary outcomes: Axial length and refractive error changes.**

- i. **Axial length:** This is defined as the axial distance from the anterior cornea to the retina along the line of sight. Myopia development and progression tends to be axial and there is strong correlation between myopia progression and changes in axial length. **Axial length measurements** can be performed using contact methods such as **ultrasound biometry** and non-contact methods such as **optical partial coherence interferometry (PCI)**, and **optical coherence tomography (OCT)**. PCI and OCT are more accurate and repeatable than ultrasound biometry and are recommended. The effect of diurnal variations, accommodation, and changes in intraocular pressure on the axial length measurement when developing the protocol should be considered.
- ii. **Refractive error measurement:** Objective refractions using an autorefractor while controlling accommodation should be used. Autorefractors have a repeatability of $\sim \pm 0.21$ D, which could encompass a good percentage of the 0.30 to 0.50 D per-year treatment effect being targeted, but autorefractors exhibit higher precision and minimize unconscious investigator bias. Open-field autorefractors are recommended to minimize variability due to residual accommodation and instrument myopia. Instruments should be validated and calibrated at regular intervals. As the standard clinical refraction is designed to generate a single end point, it can be mistakenly assumed that an eye has a single

refractive state, but due to ocular aberrations, refractive state can vary significantly across the pupil. Therefore, refraction methods that employ a known pupil location, repeatable across time, are preferred.

- b. **Secondary outcomes: Subjective information** about the child wearing experience and effectiveness of the treatment or understanding of the treatment should be assessed. **Compliance with treatment** is an important aspect contributing to the outcome and validity of results in any clinical trial. Compliance can be improved using text messaging and gamification (the process of adding games or game-like elements to something such as a task to encourage participation), collecting data on activities outside the study visits using a questionnaire/diary (such as nightly or weekly between study visits), with electronic methods improving this further. Compliance can also be supported using appropriately written **consent forms**. **Wearable technology** can also be utilized to capture behavioural/environmental data.

- III. **Exploratory outcomes:** Exploratory outcomes such as **peripheral refraction, accommodation changes with optical devices, pupillometry, anterior segment imaging, posterior segment imaging, outdoor activity/light levels, scleral and corneal biomechanics**, have been adopted to aid in the prediction of efficacy for individuals, to better understand the mechanism of control, or to investigate safety aspects.

Expected Minimum Data Set for Each Treatment Modality										
Treatment Modality	Distance Visual Acuity	Near Visual Acuity	Pupil Size	Cycloplegic Refraction	Axial Length	Amplitude of Accommodation	Contrast Sensitivity	Lens Centration	Wearing Time	Instillation Compliance
Spectacles	X	X	X	X	X	X	X	-	X	-
Soft multifocal contact lenses	X	X	X	X	X	X	X	X	X	-
Orthokeratology	X	X	X	X	X	X	X	X	X	-
Pharmaceuticals	X	X	X	X	X	X	X	-	-	X

Reference: Wolffsohn JS, Kollbaum PS, Berntsen DA, et al. IMI - Clinical Myopia Control Trials and Instrumentation Report. Invest Ophthalmol Vis Sci 2019; 60(3): M132-M60. <https://iovs.arvojournals.org/issues.aspx?issueid=937872#issueid=937872>

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Correspondence

Brien Holden Vision Institute Ltd
Level 4, North Wing, Rupert Myers Building, Gate 14 Barker Street,
University of New South Wales, UNSW NSW 2052
m.jong@bhvi.org
+612 9385 7516