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IMI – Clinical Myopia Control Trials and Instrumentation Report

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The evidence-basis based on existing myopia control trials along with the supporting academic literature were reviewed; this informed recommendations on the outcomes suggested from clinical trials aimed at slowing myopia progression to show the effectiveness of treatments and the impact on patients. These 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). The currently available instrumentation, which the literature has shown to best achieve the primary and secondary outcomes, was reviewed and critiqued. Issues relating to study design and patient selection were also identified. These findings and consensus from the International Myopia Institute members led to final recommendations to inform future instrumentation development and to guide clinical trial protocols.

Keywords: myopia control, myopia progression, clinical trial guidelines, instrumentation, recommendations

1. Introduction, Scope, and Guiding Principles

This report has identified the primary, secondary, and exploratory outcomes suggested from clinical trials for slowing myopia progression, showing the effectiveness of treatments and the impact on patients. Currently available instrumentation that the literature has shown to be the best to achieve the primary and secondary outcomes was reviewed and critiqued. Issues were also identified relating to study design and patient selection in adherence to the tenets of the Declaration of Helsinki and ethics. These findings and consensus from the International Myopia Institute members led to final recommendations to inform future instrumentation development and guide clinical trial protocols.

2. Study Design

When conducting a study to determine the efficacy of a treatment for myopia control, it is critical to utilize sound clinical trial methodology. Decisions when designing a standardized clinical trial not only minimize variability and bias, they also maximize generalizability and allow for easier comparison among studies. There are many decisions to be made when designing a clinical trial.

2.1 Study Length

The average age of myopia onset in the United States and Singapore is eight years of age, and the average age at which myopia progression is reported to cease is roughly 16 years, although progression at slower rates can also be observed in children older than 16 years.[1–3] However, age of myopia onset, rate of progression, and duration of progression vary internationally, with Asians having earlier onset, faster rates of progression, and longer duration of progression than other races.[4,5] Because myopia control interventions will be applied for multiple years throughout the time myopia is progressing, it is important that clinical trials evaluate efficacy over a long period to ensure continued efficacy beyond any initial

treatment effect.[6] The Correction of Myopia Evaluation Trial (COMET) demonstrates this point well. This large, well-conducted clinical trial evaluating the efficacy of Progressive Addition Lens spectacles versus standard spectacles, found a treatment effect after 1 year; however, the treatment effect did not continue to accumulate over the 2 subsequent years of the trial.[7] Evidence of diminishing efficacy beyond the first year was also noted in other bifocal and Progressive Addition Lens spectacle studies[8,9] and orthokeratology (OK) studies.[10]

As demonstrated, the extrapolation of a 1-year treatment effect to multiple years can lead to incorrect conclusions. To employ the best evidence-based practice, it is important that eye care providers have clinical trial research to support the multi-year use of a particular treatment. If a treatment is shown to provide an effect only over a short time period, this is also valuable information that can allow a practitioner to make an informed decision regarding when to change treatment modalities. The length of the trial must also be balanced with feasibility; as trial length increases, the ability to retain participants becomes more difficult, progression begins to slow naturally, and costs increase. For this reason, 3 years is the recommended minimum length of a clinical trial assessing the efficacy of a treatment for myopia control.

2.2 Participant Selection Criteria

This section is informed by 24 recent evidence-based papers from four categories of clinical trials. Category 1 included multifocal spectacles[9,11–14] and under-correction with single vision spectacles.[15,16] Category 2 included OK lens trials.[17–20] Category 3 included bifocal contact lenses[6,21–23] and multifocal contact lenses.[24–28] Category 4 included atropine treatment.[29–32] Studies on outdoor activities were not included because the cohorts were substantially different from those in the other four categories.

2.2.1 Refractive Error.

2.2.1.1 Spherical or Spherical Equivalent Refractive Error. Spherical refractive error was part of the inclusion criteria in categories 2 and 3, whereas spherical equivalent refractive error was mostly adopted in categories 1 and 4. Because the amount of astigmatism was limited in each trial (see Section 2.2.1.4) and the value typically is no greater than 1.50 D, the choice of whether to use spherical or spherical equivalent for the inclusion criteria was generally inconsequential. For the evaluation of myopia progression, spherical equivalent refractive error was adopted in all studies except OK studies. The use of cycloplegia is discussed in Section 2.6 and refractive error determination in Section 3.1.2.

2.2.1.2 Progression Over Period Prior to Enrollment. Four trials adopted a minimum progression rate prior to enrollment as an inclusion criteria.

One trial adopted one 0.3 D/year,[26] one 0.5 D/year,[33] one 1.0 D/year,[31] and one 0.5 D progression since the last visit.[21] Only the latter study reported that progression was assessed "based on clinical records, results of spectacle neutralization, or written prescriptions."[21] The criteria were adopted in recent trials to confirm the prevention effect among participants who have at least a minimum level of recent myopia progression. However, deciding progression on the basis of typically two "noisy" data points could lead to errors in participant selection, whereas recruiting non-progressing myopes could cause overestimation (if in the treatment group) or underestimation (if in the control group) of the treatment effect and may be considered unethical.

2.2.1.3 Astigmatism Limit. An equal number of studies adopted a maximum of 1.00 D or 1.50 D ($n = 10$ each) with two adopting 1.25 D (Table 1).

2.2.1.4 Anisometropia. Most studies ($n = 8$) have adopted a maximum permissible limit of 1.50 D, but others have selected $\leq$1.00 D ($n = 5$), $\leq$1.25 D ($n = 1$), or $\leq$2.00 D ($n = 2$) (Table 1).

2.2.2 Age. While one study adopted a minimum age of 5 years, most adopted a minimum of 6 years of age. Most trials adopted 12 years as the maximum age ($n = 6$), but others ranged from 7 years ($n = 2$) to 18 years ($n = 2$). There appears to be no particular trend within inclusion criteria for the modality of intervention (Table 1).

2.2.3 Previous Optical Correction. Previous optical correction may affect the efficacy of a myopia control intervention. Generally, spectacles and monofocal soft contact lens (SCL) are accepted as options for previous correction; however, in an under-correction spectacle study,[16] participants were excluded who had worn an under-corrected spectacle prescription previously (i.e., had not been prescribed their full myopic refractive correction). Rigid contact lens wearers were specifically excluded, mostly in studies involving multifocal or bifocal (SCL) and OK studies.

2.2.4 Previous Myopia Treatment. Patients with a history of previous myopia control treatment were excluded in all studies.

2.2.5 Exclusion Criteria. Participants with ocular pathology, such as retinal detachment, were excluded in all studies, as were patients with strabismus. Studies generally exclude participants who are on medications that may affect pupil size, accommodation, or have an impact on the ocular surface (such as allergy medications). The literature does not always outline specific exclusion criteria other than prescription range. Systemic disease that may affect vision, vision development, or contact lens wear (such as diabetes and Down syndrome), were explicitly excluded in a recent study (Table 2).[28]

2.3 Appropriate Control Group

A placebo-controlled clinical trial in which participants do not know their group assignment is generally considered the gold standard. Ideally, the control or sham (placebo) treatment cannot be distinguished from the active treatment with the only difference between the treatment and control being a hypothesized intervention, such as an optical design or active pharmaceutical agent.[35,36] That said, the most appropriate control group will depend on the intervention being studied. Studies with no control group are unable to demonstrate treatment efficacy; for example, the rate of myopia progression decreases naturally with age, so it is not possible to distinguish between naturally declining progression and reduced progression attributable to the treatment, without a simultaneously conducted control group.[1,4] Likewise, studies utilizing historical control groups also allow the introduction of unknown sources of bias. In several studies, historical control groups have been used (Table 3). An appropriate control group manages potential sources of bias, alleviating many of these concerns. 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. It is often a challenge to keep participants in a control group, particularly if the efficacy of the treatment group becomes or is perceived to be established.

2.3.1 Pharmaceutical Studies. The recommended placebo is the vehicle used in the active treatment intervention but without the active pharmaceutical agent being evaluated in the treatment group. By using a control that differs from the treatment drug's active ingredient, any effect can be isolated to the specific molecule being evaluated. When this is not possible, the control treatment should mirror the active treatment medication as closely as possible. In either case,

Table 1. Selection Criteria in Recent Myopia Control Clinical Trials

Author, Year	Intervention	SER, Min to Max (D)	Cyclo-plegia	Ast Limit (D)	Aniso Limit (D)	VA Min	Age, Min to Max (y)
Gwiazda et al., 2002[12]	Spectacle (multifocal)	−4.50 to −1.25	Y	1.50	1.00	20/32	6 to 11
Edwards et al., 2002[11]	Spectacle (multifocal)	−4.50 to −1.25	Y	1.50	1.50	20/20	7 to 10.5
Hasebe et al., 2008[13]	Spectacle (multifocal)	−6.00 to −1.25	N	1.50	1.50	20/20	6 to 12
COMET group* 2011[9]	Spectacle (multifocal)	−0.75 to −2.50 and esophoria ≥2 PD @ 33 cm	Y	1.50	1.00	20/20	8 to <12
Berntsen et al., 2012[34]	Spectacle (progressive addition lens)	−4.50 to −0.75 in each meridian with esophoria if more myopic than −2.25 SER	Y	2.00	2.00	20/30	6 to 11
Hasebe et al., 2014[14]	Spectacle (multifocal)	−4.50 to −0.50	Y	1.50	1.50	20/30	6 to 12
Adler et al., 2006[15]	Spectacle (under corr.)	−6.00 to −0.50	N	1.50	1.50	20/30 (6/9)	6 to 15
Sun et al., 2017[16]	Spectacle (under corr.)	−6.00 to −0.50	Y	1.50	1.00	20/20	12 (grade 7)
Kakita et al., 2011[18]	Orthokeratology	−10.0 to −0.50	N	1.50	1.50	20/20	8 to 16
Walline et al., 2009[17]	Orthokeratology	−4.00 to −0.75	Y	1.00	—	20/20	8 to 11
Cho et al., 2012[19]	Orthokeratology	−4.50 to −0.50	N	1.25	1.50	20/20	6 to 10
Santodomingo-Rubido et al., 2012[20]	Orthokeratology	−4.00 to −0.75	Y	1.00	—	20/20	6 to 12
Lam et al., 2014[22]	SCL (concentric bifocal)	−5.00 to −1.00	Y	1.00	1.25	20/20	8 to 12
Aller et al., 2016[21]	SCL (concentric bifocal)	−6.00 to −0.50	Y	1.00	2.00	20/20	8 to 18
Pomeda et al., 2017[23]	SCL (concentric bifocal)	−4.00 to −0.75	Y	1.00	1.00	20/25	8 to 12
Chamberlain et al., 2017[6]	SCL (concentric bifocal)	−4.00 to −0.75	Y	1.00	1.00	20/25	8 to 12
Walline et al., 2013[24]	SCL (multifocal)	−6.00 to −1.00	Y	1.00	1.00	20/20	8 to 11
Fujikado et al., 2014[25]	SCL (multifocal)	−3.50 to −1.00	Y	1.00	1.00	20/20	10 to 16
Paune et al., 2015[26]	SCL (multifocal)	−7.00 to −0.75	Y	1.25	1.00	20/20	9 to 16
Cheng et al., 2016[27]	SCL (multifocal)	−4.00 to −0.75	Y	1.00	1.00	20/25	8 to 11
Walline et al., 2017[28]	SCL (multifocal)	−5.00 to −0.75	Y	1.00	2.00	20/25	7 to 11
Chua et al., 2006[29]	Atropine (1.00%)	−6.00 to −1.00	Y	1.50	1.50	20/32	6 to 12
Chia et al., 2012[30]	Atropine (0.01%)	< −2.00	Y	1.50	NR	20/32	6 to 12
Polling et al., 2016[31]	Atropine (0.50%)	≤ −3.00	Y	NR	NR	NR	5 to 10
Wang et al., 2017[32]	Atropine (0.50%)	−2.00 to −0.50	Y	NR	NR	NR	8 to 11

under corr., under correction; SER, spherical equivalent refractive error; AST, astigmatism; ANISO, anisometropia; VA, visual acuity; PD, prism dioptres; NR, not reported; D, dioptre; y, years.

* The correction of myopia evaluation trial.

Table 2. Typical Inclusion/Exclusion Criteria, Although Should Be Altered to Address Specific Study Hypothesis

Selection Criteria
Refractive error
Cyclopleged spherical or Spherical Equivalent myopia of at least −0.75 D
Astigmatism ≤1.00 D
Anisometropia ≤1.50 D
Age
6–12 years
Visual acuity
20/20 minimum
Exclusion Criteria
Previous RGP wear
History of previous myopia control treatment
Ocular pathology
Binocular vision anomaly
Medications that may affect pupil size, accommodation or have an impact on ocular surface
Systemic disease that may affect vision, vision development or the treatment modality

the administration regimen should be the same whether a participant is in a treatment or control group. In atropine studies, past studies have applied a vehicle placebo to the control group (Table 3).

2.3.2 Contact Lens Studies. The best choice for a control group depends on the treatment modality being evaluated. One prominent theory of myopia control hypothesizes that peripheral myopic defocus slows progression.[4] Both single vision spectacles and spherical SCL change peripheral defocus from the uncorrected state by amounts that vary between lens designs and by lens power.[37–39] A control contact lens made of the same material is ideal and, if possible, the optics of the control lens should not change peripheral defocus. However, current options change the peripheral refraction and spherical aberration[40,41] so, ideally, the "optimal" lens may be one with known levels of spherical aberration that do not vary with lens power. In multifocal or bifocal SCL studies, control groups have generally used single-vision SCL (Table 3). Two randomized controlled trials have shown no clinically meaningful difference in myopia progression between single vision contact lenses and single vision spectacles.[42,43] However, such studies do not allow participant masking.

2.3.3 OK Studies. There is no ideal control group that allows double masking. Spherical gas permeable contact lenses, SCL, or spectacles must be worn during the day to correct vision, unlike OK lenses where the child typically

Table 3. Control Group, Randomization, and Masking

Author, Year	Intervention	Control	Randomization	Stratification	Masking
Gwiazda et al., 2003[7]	Spectacle (multifocal)	Spectacle (SV)	Y	N	Y
Hasebe et al., 2008[13]	Spectacle (multifocal)	Spectacle (SV)	Y	N	Y
Edwards et al., 2002[11]	Spectacle (multifocal)	Spectacle (SV)	Y	N	Y
Berntsen et al., 2012[34]	Spectacle (Progressive Addition Lens)	Spectacle (SV)	Y	Y	Y
Hasebe et al., 2014[14]	Spectacle (multifocal)	Spectacle (SV)	Y	N	Y
Adler et al., 2006[15]	Spectacle (under corr.)	Spectacle (SV)	Y	N	N
Sun et al., 2017[16]	Spectacle (under corr.)	Spectacle (SV)	N	N	N
Cho et al., 2012[19]	OK	Spectacle (SV)	Y	N	N
Kakita et al., 2011[18]	OK	Spectacle (SV)	N	N	N
Santodomingo-Rubido et al., 2012[20]	OK	Spectacle (SV)	N	N	N
Walline et al., 2009[17]	OK	Historical (SV SCL)	N	N	N
Pomeda et al., 2017[23]	SCL (concentric bifocal)	Spectacle (SV)	Y	Y	N
Chamberlain et al., 2017[6]	SCL (concentric bifocal)	SCL	Y	Y	Y
Aller et al., 2016[21]	SCL (concentric bifocal)	SCL (SV)	Y	Y	Y
Lam et al., 2014[22]	SCL (concentric bifocal)	SCL (SV)	Y	N	Y
Walline et al., 2017[28]	SCL (Multifocal)	SCL (SV)	Y	Y	Y
Cheng et al., 2016[27]	SCL (Multifocal)	SCL (SV)	Y	Y	Y
Fujikado et al., 2014[25]	SCL (Multifocal)	SCL (SV)	Y	Y	N
Walline et al., 2013[24]	SCL (Multifocal)	Historical (SV SCL)	N	N	N
Paune et al., 2015[26]	SCL (Multifocal)	SCL (SV)	N	N	N
Wang et al., 2017[32]	Atropine (0.50%)	Placebo	Y	Y	Y
Polling et al., 2016[31]	Atropine (0.50%)	None	N	N	N
Chua et al., 2006[29]	Atropine (1.00%)	Placebo	Y	N	Y
Chia et al., 2012[30]	Atropine (0.01%)	Historical (Placebo)	Y	N	N

SV, single vision; under corr, under correction; OK, orthokeratology; SCL, soft contact lens; Y, yes; N, no.

wears the contact lens at night and needs no correction during the day to see clearly after removal. Alignment fitted gas permeable contact lenses can flatten the cornea and thus contaminate the apparent influence of the lens on refractive error.[44] For these reasons, spectacle lenses are adequate control lenses. There is also evidence that spherical surfaced SCL do not alter myopia progression, making them a viable option as well[42]; however, even these lenses (brand identified by personal communication with the principal investigator) had levels of spherical aberration that varied with lens power (minus lenses inducing negative spherical aberration). Therefore, presumably, the optics of the lenses change peripheral defocus, so not every person evaluated had "the same" control. In previous multifocal spectacle studies, control groups generally used single vision spectacle lenses (Table 3).

2.3.4 Multifocal Spectacle Studies. Control groups generally used single-vision spectacle lenses. It is not possible to mask bifocal spectacle lenses.

2.4 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 group.[35,36] Randomization assignments should not be available to investigators in advance and should be accessible only after the investigator has confirmed the participant's eligibility to be enrolled in the clinical trial; this is best 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 race/ethnicity—should be considered. Stratification should be limited to a few key factors. To avoid detrimental effects from over-stratifying, a statistician should always be consulted during the planning stage of any study to determine how many stratification factors can be considered based on the planned size of the study. To help ensure more equal allocation of important stratification factors between the treatment and control group, block randomization using random, even, small block sizes should be employed. Randomization schemes should be generated using appropriate statistical software.

An intent-to-treat philosophy should be used when analyzing data. Once a participant is randomized to a particular group, that participant should always be analyzed as part of the assigned treatment group, even if the participant later discontinues treatment or changes treatment groups during the study. The intent-to-treat principle preserves randomization and prevents the introduction of bias during analyses. A per-protocol population is a subset of the intent-to-treat population who completed the study in accordance with the protocol. Users of this intent-to-treat philosophy should be aware that treatment effects might be conservative (e.g., due to noncompliance), and interpretation of endpoints might be difficult if large numbers of participants change over to the opposite treatment arm.

In most previous studies, randomized controlled trials were adopted. Three studies using OK did not use randomization.[17,18,20] These studies had inclusion criteria, but participants and their parents had the choice between OK or single vision spectacles. Several studies were stratified by age or refraction (Table 2).

2.5 Masking

Clinical trials should utilize double masking whenever possible to minimize the potential for bias (i.e., both the participant and the examiner collecting primary outcome data should be masked to the participant's treatment assignment). Masking of the participant helps ensure they remain compliant with their assigned treatment and do not change their behavior in a way that might influence the outcome. In the case of OK, participant masking is not possible (see Section 2.3). At a minimum, investigators who assess study outcomes should

always be masked to minimize the introduction of unintended bias by the investigator during the study due to consciously or subconsciously treating participants differently.[35,36]

In the previous studies for spectacle, SCL, and atropine, masking was usually employed. In OK studies, masking could not be adopted as the control group used spectacles. However, examiners who were masked with regard to the lens assignments performed portions of the clinical examinations, including refraction, axial length measurement, and prescribing spectacles. An unmasked investigator performed allocation using a random number table or a computer software program that generated a random sequence.

2.6 Cycloplegia

Cycloplegia should be used when measuring primary outcomes in studies of myopia progression to minimize variability. The recommended regimen that has been used in multiple clinical trials is two drops of 1% tropicamide separated by 5 minutes with primary outcome measures commencing 30 minutes after the first drop of tropicamide is instilled. This protocol has been previously evaluated by Manny and colleagues[45] in an ethnically diverse cohort of children enrolled in the Correction of Myopia Evaluation Trial (COMET) and determined to be an appropriate method for cycloplegia. Residual accommodation was found to be small (0.38 ± 0.41 D). Work comparing the effects of cyclopentolate and tropicamide also found no meaningful difference in measured refractive error between agents 30 minutes after instillation.[46] Given the unnecessarily longer-lasting cycloplegic and mydriatic effects of cyclopentolate versus 1% tropicamide as well as minimal additional gain in cycloplegia with cyclopentolate in myopic children, 1% tropicamide is recommended in optical treatment studies. If used consistently throughout the study, 1% tropicamide provides adequate cycloplegia for outcome measures while balancing the importance of retaining children in longitudinal clinical trials, thereby minimizing the duration of mydriasis and cycloplegia upon completion of each study visit. As atropine also causes cycloplegia, the use of a cycloplegic agent for refraction with less potency could confound the assessment of the treatment effect. In studies involving pharmaceutical interventions, the baseline refractive error and biometry measurements used to calculate the change in myopia progression and axial growth should be performed shortly after the child has begun treatment using their assigned intervention so that the baseline also has the combined effect of the cycloplegics.

2.7 Assessment of Rebound

The question of rebound after ceasing treatment is important to consider for any myopia control treatment. For a treatment to be beneficial, the effect must be maintained after treatment is stopped. Studies of atropine demonstrate a rebound (accelerated eye growth) after discontinuing use and is greatest with higher concentrations of atropine.[47] While studies utilizing multifocal spectacles and SCL have not produced evidence of a rebound,[34] it is possible that more efficacious optical treatments might be prone to more accelerated eye growth after discontinuation of treatment.

In studies aimed to evaluate the potential presence of accelerated progression after ceasing treatment, the minimum recommended time period over which a rebound effect should be evaluated is 1 year due to naturally occurring seasonal variations in myopia progression (slower growth in the summer versus the winter).[48] Assessing for a rebound effect is best accomplished in a clinical trial in which children assigned to the treatment group are switched to the control treatment, with all children in the trial then followed using the control treatment. However, ethical implications of this approach should be considered.

2.8 Safety

2.8.1 Standardized Adverse Event Reporting. With any new or developing medical technology, it is important to continuously evaluate the cost versus benefit of the technology. For example, for children wearing SCLs, it should be considered whether the benefits provided by the contact lens (such as in correcting vision or controlling myopia progression) outweigh any ocular health risks.

Thirty collaborating centers of the World Health Organization[49] have established common definitions of terms related to adverse event reporting. Specifically, 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." Therefore, an adverse event can "be any unfavorable and unintended sign," symptom or disease associated with the use of a medical device or drug.[50] It is necessary to make a risk-benefit judgment for approval or use of a product; to do this effectively, the classification and reporting of adverse events should occur in a standardized manner and timeframe. If occurring within a study, this event information must also be communicated to the manufacturer, care provider, patient constituencies, and institutional review board.

Contact lens adverse events can be classified in several ways, such as graphically represented by a decision tree.[51] Specifically, an adverse event should first be classified as either "serious" or "non-serious." Serious events are those that are life threatening, require inpatient or prolonged hospitalization, or may cause permanent impairment or damage. An important serious adverse event related to the eye and contact lens use is the occurrence of microbial keratitis. Non-serious events may include red eye and discomfort (see Section 2.8.2). Adverse events are often further subdivided in terms of severity (such as mild, moderate, or severe), device-related (often referred to as a "device effect"), and whether it was unanticipated versus anticipated (often referred to as "not unanticipated" because anticipated suggests that an unfavorable occurrence is likely to occur). Specifically, adverse events at all times should be differentiated from normal or anticipated consequences of contact lens use, such as minor eye dryness[52] and changes in corneal morphology.[53–55]

Many governmental organizations around the globe protect consumers by creating device reporting methods. For example, in the United States, the U.S. Food and Drug Administration (FDA) Medical Device Reporting (MDR) regulation (21 CFR 803) contains mandatory requirements for manufacturers, importers, and device user facilities to report certain device-related adverse events and product problems. The FDA also encourages healthcare professionals, patients, caregivers, and consumers to submit voluntary reports of significant adverse events or product problems with medical products to MedWatch, the FDA's Safety Information and Adverse Event Reporting Program.[56] Other organizations around the globe have similar regulations and provide similar reporting systems, such as Health Canada and the Australian government's Therapeutic Goods Administration.

Infiltrative adverse events among patients of all ages and lens types have been reported to occur at a low incidence (such as corneal infiltrative event incidence of 21 per 10,000 SCL wearing years).[57,58] Specifically, the incidence of events in children has not been found to be higher than that in adults. In fact, in the 8- to 11-year age range (a range where myopia control lenses might become very commonly utilized),

estimated incidence of events is actually lower than in adults.[58] Monitoring, classification, and reporting methods should be specifically outlined in any research study. Additionally, practitioners should inform participants and parents of pediatric wearers about normally anticipated consequences of contact lens wear, potential adverse events, and what to do if adverse events occur. Participants (and, in case of child participants, their parents) should be informed about the necessity of reporting adverse events.

Pharmaceutical treatment of myopia is associated with short-term effects such as photophobia and possible long-term effects such as light-induced retinal damage or cataract formation.[59] The use of atropine for myopia control (0.5%) resulted in over 80% of children having adverse events (whether reported by the parents or the children themselves), such as photophobia (60%–82%), systemic flushes (3%–6%), infections such as conjunctivitis/blepharitis (0%–3%), headaches (7% reported by children who maintained therapy compared to 31% in those that ceased therapy), and reading problems (~25% in those who maintained therapy compared to ~80% in those that ceased therapy).[31] Other studies have reported no serious adverse events.[29,32] For pirenzepine ophthalmic gel (2%), similar mild to moderate adverse events were experienced in one of two studies, with serious adverse events deemed unrelated to the treatment.[60,61]

2.8.2 Ocular Health. At the outset of any clinical trial, a series of assessments determine baseline data for trial participants. Baseline information that is collected in a standardized way can be used for various reasons, including characterization of participants, analysis of outcomes based on baseline measurements, and treatment effects based on presenting characteristics.[62] Examples can include presence or absence of heterophoria, baseline amount of myopia, and accommodative function. These may inform exclusion criteria or be used to assess the impact of a myopia control treatment on ocular physiology. Evaluation of the posterior pole is critical for all myopia control studies to identify any retinal changes or pre-existing retinal conditions that may exclude participation in a clinical trial, require a participant to withdraw from a clinical trial, or require the participant to be referred for further assessment. Fundus abnormalities in asymptomatic patients are uncommon. It has been estimated that fundus anomalies occur in approximately 2.5% of patients under the age of 20, with less than 1% of those findings being clinically significant.[63] It is well known that myopia is associated with an increased risk of many ocular diseases, including myopic maculopathy, retinal detachment, glaucoma, and cataract.[64–67] These risk factors increase with increasing age and increasing magnitude of myopic refractive error. In a study on myopic maculopathy, the incidence in patients with a prescription less myopic than 5.0 D was 0.42%, compared with 25.3% in patients with more myopic prescriptions.[68] Findings have been similar for the risk of retinal detachments, with an increased risk in patients with more myopic prescriptions, but even lower levels of myopia (less myopic than −3.0 D) have been shown to have a three times increased risk of retinal detachment compared to emmetropic patients.[69] However, all levels of myopia increase the risk of retinal pathology, so there is no physiologically safe (or non-pathological) level of myopia (see accompanying IMI – Defining and Classifying Myopia Report).[70,87]

A dilated fundus examination should be performed on participants at baseline and subsequent annual or periodic visits. In a study involving pediatric patients, 51% of participants had one or more peripheral anomalies (albeit mainly clinically insignificant) that were detected in a dilated fundus examination that were otherwise undetected in a nondilated examination.[71] The use of a binocular indirect ophthalmoscope (BIO) is considered the gold-standard for assessing the peripheral fundus. Typically, a 20 D lens is used in conjunction with the BIO, but for younger patients, a 28 D lens can be more useful as it gives a slightly larger field of view.[72]

A clinical trial involving contact lenses or pharmaceuticals will require a full anterior assessment at each visit. The slit lamp biomicroscope offers a variety of illumination techniques and magnification options to examine the anterior chamber.[73,74] A full slit lamp examination utilizes various techniques in a coordinated, systematic way to ensure a full examination of all relevant anterior structures; the results should be recorded with an appropriate grading technique.[75]

Associations have been reported between myopia progression, higher levels of esophoria, and accommodative lag in some studies (see Sections 3.3.2 and 3.3.3), and binocular vision problems are relatively common in children[76,77]; thus, it is important to perform a binocular vision assessment at baseline (potentially as part of exclusion criteria to ensure they are not a confounding factor) and at periodic times throughout a myopia control study, such as during annual assessments. Typically, participants with a manifest strabismus would be precluded from participating in a myopia control clinical study, although this is not always specifically stated in the reported exclusion criteria (see Section 2.5).

2.8.3 Vision.

2.8.3.1 Visual Acuity. LogMAR visual acuity is measured in virtually every clinical trial assessing myopia control treatments. It can be both an inclusion/exclusion criterion (participants need to have a visual acuity better than an arbitrary value) and to assess any negative (safety) impact of optical, pharmaceutical, or environmental modifications both during (reduced vision could affect educational performance and mobility) and after treatment (permanent visual loss would be a serious adverse event; see Section 2.8.1). When measuring visual acuity, considerations include what correction should be worn (unaided, mean spherical equivalent or full spherocylindrical correction, habitual visual correction or the device), whether the measures are monocular or binocular and the target distance (far, near, or a full defocus curve). Contrast sensitivity is measured in fewer studies, but may be more sensitive to detect reductions in functional vision.[78] Some studies have shown small reductions in high-contrast visual acuity and contrast sensitivity when wearing off-label multifocal contact lenses,[79] while other studies showed no significant effects of other multifocal contact lens designs on visual acuity or contrast sensitivity.[80,81] Low dose (0.01%) atropine has shown no significant effect on visual acuity in young adults over a 5-day period.[82]

Some studies use Snellen visual acuity charts and convert to logMAR, negating the benefits of the standardization and uniformity of logMAR charts.[83] Using Snellen visual acuity is discouraged for reporting outcomes; studies collecting Snellen acuity should not convert these to logMAR for reporting, which gives the false perception that logMAR was collected. There is considerable variation in the way visual acuity measurements are expressed (logMAR and decimal notation can easily be confused), and frequently the charts and the procedures used for visual acuity testing are inadequately described.[84] As methodology can markedly affect visual acuity scores, studies should provide enough detail about their methodologies to allow others to replicate and benchmark against them.

2.8.3.2 Functional Vision. Reading speed has been found to correlate better with vision related quality of life (satisfaction with functional vision) than does traditional high contrast visual acuity. However, few myopia control studies have used reading speed, perhaps due to the time taken to conduct the measurement. Of the studies to assess reading speed to date,

no difference from controls was found with an off-label multifocal contact lens design[79] or with short-term use of atropine 0.01% in Caucasian young adults.[82] Other aspects of near work are generally captured in questionnaires[85] (see Section 3.2.1).

2.8.4 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. However, few studies have examined the potential adverse effect of dysphotopsia associated with myopia control strategies. Loughman and Flitcroft assessed glare, albeit in a young adult population over a 5-day use period, 0.01% atropine, showing a slight increase in symptoms, but no impact on quality of life.[82] A recent paper examined the role of short-wavelength filtering lenses in delaying myopia progression and amelioration of asthenopia in juveniles, finding no effect over a year's duration on refraction or axial length compared to controls, but a reduction of the effect of glare on contrast sensitivity.[86] Future myopia control studies should elicit whether dysphotopsia has been increased by the treatment strategy.

2.9 Clinically Meaningful Effect

It is important that similar reporting criteria are utilized across studies to maximize the comparability of results. The definition of a clinically meaningful effect is also important for determining success of any myopia treatment. Another important question is how large a treatment effect is needed in each year of a multi-year clinical trial to be considered meaningful.

The mean and standard deviation of the difference in progression between groups should be reported for comparability to previously published myopia studies, as well as a thorough description of the groups and any matching. In addition to reporting *P* values, it is important that outcome papers include the 95% confidence interval for any effect reported; this allows readers to ascertain the true range of treatment effect. When stating the percent reduction in myopia progression or axial elongation between a treatment and control group, previous studies (see Section 2.1) have reported treatment effects in the first study year that did not accrue in subsequent years; therefore, it is critical that the authors report the time period over which that reduction occurred (e.g., over 1 year or 3 years). No specific minimum percent reduction in myopia progression has been published for a treatment effect to be considered clinically meaningful. Any percent reduction threshold could vary based on multiple other factors, including duration of treatment, sample population, and study design considerations. However, some clinicians anecdotally report roughly a 40% reduction in progression over 3 years as clinically meaningful to them. That said, evidence shows that any reduction in progression can be beneficial.[70] Of course, it is important to factor the relative risk of the treatment versus the reduction in risk provided by reduction in myopia. For example, a treatment with very low risk of adverse event may have a different minimum acceptable reduction than one with a higher risk of adverse event (Fig. 1). A thorough long-term, risk-benefit analysis is necessary. It is also notable that some children respond to treatment while others do not. Currently, there seems to be no way of predicting whether a particular child will or will not respond. While other ways of evaluating efficacy—for example, the percentage of children who had a reduction in myopia progression of 50% compared to the rate of progression in the control group—may provide additional information beyond the traditional mean ± SD and 95% confidence interval, any arbitrary threshold allows researchers to find a suitable analysis approach. High myopia (as defined by the IMI – Defining and Classifying Myopia Report[87]) could be taken as a standard way to discuss how many people avoid developing high myopia as the result of applying a particular management strategy.

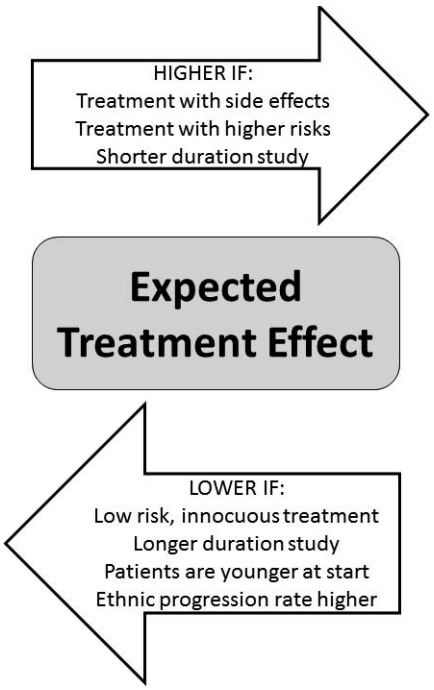

FIGURE 1. Schematic of considerations that influence the clinically meaningful effect size.

2.10 Sample Size

Sample size based on the axial length effect size with the different modalities of myopia control treatment are outlined in Table 4. In many cases, key information was missing from publications and personal communication with the principal investigator was required to gain additional statistics.

3. Clinical Trial Outcomes and Related Instrumentation

3.1 Primary Outcomes

Clinical trials represent a crucial source of information to guide the application of basic, clinical, and translational research toward the health benefit of patients. These trials test a hypothesis following a chosen treatment. A primary outcome is arriving at a decision on the overall results of the study, specifically whether the hypothesis tested is fulfilled.[88] Clinically relevant primary outcomes should relate the tested treatment directly to the patient's health and be related to disease scales. Therefore, the primary outcome of a clinical trial could be a risk/preventative factor for a disease and be sensitive enough to detect the degree of change expected from the intervention.[89] Coster proposes choosing outcome measures through creation of a causal model: "The causal model makes explicit the researcher's thinking about how the intervention is expected to achieve its results—that is, what the hypothesized mechanism of change is and in which aspects of the person's life changes are most likely to be evident."[89]

Table 4. Sample Size Calculations for Different Modalities of Myopia Control Treatment Based on Axial Length Effect Size

Intervention	Author, Year	Timescale	AxL Mean diff (SD)	AxL Min Sample Size Per Group	Rx Mean Diff (SD)	Rx Min Sample Size Per Group
Spectacles multifocal	Gwiazda et al., 2003[7]	3 years	0.11 mm (SE 0.03)	125	0.20D (SE 0.08)	333
	Hasebe et al., 2014[14]	2 years	0.082 mm (0.05)	268	0.27 (0.11)	157
Orthokeratology	Kakita et al., 2011[18]	2 years	0.22 mm (0.26)	15–99	NA	
	Walline et al., 2009[17]	2 years	0.32 mm (1.12)		NA	
	Santodomingo et al., 2012[20]	2 years	0.22 mm (not reported)		NA	
	Cho and Cheung, 2012[19]	2 years	0.27 mm (0.26)		NA	
Concentric bifocal SCL	Lam et al., 2014[22]	2 years	0.11 mm (not reported)	13–69	0.38D (not reported)*	9–?
	Aller et al., 2016[21]	1 year	0.19 mm (not reported)		0.57D (not reported)	
	Pomeda et al., 2017[23]	2 years	0.16 mm (not reported)		0.29D (not reported)	
	Chamberlain et al., 2017[6]	3 years	0.28 mm (SE 0.04)		0.67D (SE 0.09)	
Multifocal SCLs	Walline et al., 2017[28]	2 years	0.13 mm (SE 0.04)	16–51	0.52D (SE 0.06)	7–60
	Fujikado et al., 2014[25]	1 year	0.05 mm		0.22D	
	Paune et al., 2015[26]	2 years	0.14 mm		0.42D	
	Cheng et al., 2016[27]	1 year	0.14 mm 95%CI rep		0.14D 95%CI rep	
Atropine 1%	Chua et al., 2006[29]	2 years	0.40 mm 95%CI	15	0.92D 95%CI	16
Atropine 0.01%	Chia et al., 2012[30]	2 years	No control group		No control group	

Sample size calculation was based on 2 sample *t*-test comparison with 80% power and $P < 0.05$ significance level (http://www.statisticalsolutions.net/pssTtest_calc.php). SD calculated from SE and *n* where SE reported. Some cases 95%CI have been reported and not SD or SE. NA, data not available; AxL, axial length; Rx, refractive error; SD, standard deviation; Diff, difference; Min, minimum.

* 5 or more hours wearing time per day.

Clinical trials in the research field of myopia have utilized mainly refractive error and axial length as primary outcome measures, regardless of the intervention: OK,[10,17–19,90–92] atropine,[30,47,93] or bifocal contact lenses.[22,80,94] Additional secondary outcome measures, such as peripheral refraction, may be considered depending on the hypothesis being tested.[28] Overall, refractive changes are highly correlated to eye growth despite the type of myopia control intervention: under-correction,[95] multifocal/bifocal spectacles versus single vision spectacles,[7,13,33,96,97] or bifocal contact lenses versus single vision.[21] However, this is not the case in all studies.[98]

Early myopia control clinical studies did not measure and monitor axial elongation,[99,100] and those that used ultrasonography would have been limited by the resolution of this technique (~0.30 D),[101] making refractive error the preferred outcome measure in earlier studies. More recently, the measurement of the biometric components of the eye has become more widely included and is a key measurement in myopia control clinics, partly due to the non-invasive nature and improved resolution (~0.03 D) of the interferometry measurements for axial length (see Section 3.1.1).[101,102] Participantive refraction is more variable than autorefraction, despite being considered the gold standard for clinical refraction.[103] Changes in refractive error may occur due to changes in corneal curvature, so when refractive error needs to be used as the primary outcome measure, corneal curvature should be measured to help with data interpretation.[104] Overnight OK purposely alters corneal topography to target emmetropia during waking hours, so axial length can be the only primary outcome measure for the myopia control aspect of OK myopia control studies.

The advantages of using axial elongation versus refractive error as the primary outcome measure relates to the direct relationship between the excessive growth of the myopic eye and the associated risk for posterior pole complications, although the two are strongly correlated.[105–108] The incidence of various myopia-related complications (such as temporal crescents, posterior staphyloma, and chorioretinal atrophy) increases in parallel with axial length.[109] Highly myopic eyes (axial length ≥27 mm) can show macular Bruch's membrane defects associated with complete loss of retinal pigment epithelium and choriocapillaris, large choroidal vessels, and marked reduction of photoreceptors, which are strongly associated with increased axial length.[110,111] In addition to studies in human eyes, experimental myopia induced in fish, avian, mammal, and primate eyes is also characterized by axial elongation.[112–120] Axial elongation of the eye triggers chorioretinal stretching and thinning of the choroid, retina, and scleral wall,[121–126] and increases the risk of developing posterior staphyloma[109] as well as peripheral retinal changes such as lattice degeneration, pavingstone degeneration, white with or without pressure, and retinal holes and tears.[127] Since even moderate amounts of myopia significantly increase the odds of vision-threatening conditions,[70] the end goal of all clinical trials for myopia control should be reduction of axial elongation (associated with posterior pole complications) to have the greatest effect on myopic patients' health status. This way, a clinically relevant primary outcome is chosen directly related to patients' health and disease scales, which could be used as a risk/preventative factor for the disease.

3.1.1 Axial Length Measurement. Axial length is typically defined as the axial distance from the anterior cornea to the retina (exact location within retina varies by technique) along the line of sight, and this ocular biometric measure is considered one of the principal biometric correlates of spherical equivalent refractive error. Numerous studies have established a strong correlation between the eye's axial length and its refractive error.[105–108] Myopia development and progression usually occur due to excessive axial elongation of the eye, as evidenced by the strong correlation observed between changes in refractive error (i.e., myopia progression) and changes in axial length (i.e., axial growth of the eye).[7,96,128] For these reasons, measurements of the change in axial length in an individual are commonly used as the primary outcome measure of myopia clinical trials in the myopia research field.

A range of physiological factors have been documented that lead to small, but significant, short-term/transient changes in axial length measures: diurnal variations,[129,130] accommodation[131,132] and changes in intraocular pressure.[133,134] Clinical

trials assessing axial length should therefore consider the potential influence of these factors in protocol development, providing the most reliable measures of axial length and hence comparisons within and between groups. For example, ideally, axial length measures collected at approximately the same time of day would limit the potential confounding influence of diurnal variations (although these are small)[135]; however, this must be balanced by retaining all participants enrolled in a clinical trial and seeing them for scheduled visits within a defined visit window. A range of instruments are currently available for assessment of axial length, and these measurement techniques can be divided into ultrasound and optical based biometry methods.[101,102]

3.1.1.1 Ultrasound Biometry. Ultrasonographic methods for the measurement of intraocular distances were developed in the 1950s and 1960s,[136,137] and some early studies in the myopia field used ultrasound-based techniques for assessment of axial length.[138,139] Ultrasound biometry involves a transducer directing high frequency (typically 10 mHz in ocular ultrasound) pulsed sound waves into the eye and recording echoes of these waves reflected from the ocular structures. The time delay of these echoes is converted into a geometric distance through knowledge of the velocity of sound in the various ocular media. Axial length measurements from ultrasound instruments are defined as the distance from the anterior cornea to the inner limiting membrane of the retina.

The properties of ultrasound wave require that the ultrasound transducer be in contact with the eye, either directly (in the case of applanation ultrasound) or indirectly (via immersion of the anterior eye in saline solution for immersion ultrasound) to take measurements. Studies comparing applanation and immersion ultrasound techniques typically find lower axial length readings with applanation methods, which can be attributed to compression of the cornea, leading to a reduction in the corneal thickness or anterior chamber depth (ACD) and, hence, axial length.[140,141] Ultrasound axial biometry devices typically provide measurements of axial length with an accuracy of approximately 0.1 mm.[140] Reports of repeatability with A-scan ultrasonography demonstrate 95% limits of agreement for test-retest repeatability in the range of ±0.2 to ±0.3 mm for measures of axial length.[142–144] Considering that a 0.1 mm change in axial length is the equivalent of a refractive change of ∼0.3 D, the ability of ultrasound methods to detect small magnitude changes in axial length is limited. This relatively coarse repeatability, the need for corneal anesthesia and contact with the eye, and dependence on operator expertise to achieve axial alignment of the transducer[145] associated with ultrasound biometry methods have prompted development of alternative measurement techniques based on optical principles. These newer methods have largely superseded ultrasound measurements in the myopia research field.

3.1.1.2 Optical Biometry. The limitations associated with ultrasound techniques provided the catalyst for development of optical biometry methods, based upon optical partial coherence interferometry (PCI) that provide axial length measures without the need for corneal contact.[146,147] In this method, two partially coherent laser beams are directed into the eye and reflected back from the ocular tissues. Interference between the two reflected laser beams forms interference fringes with peaks corresponding to the eye's surfaces. The optical path length between these interference peaks can be converted into geometric distance based on the presumed refractive index of the ocular structures. Interferometry methods define axial length as the distance between the anterior cornea and the retinal pigment epithelium. It is worth noting that the use of an assumed average total eye refractive index will result in some overestimation of axial length when measures are collected during accommodation (an error of ∼0.02 mm was estimated to occur for measures during 10.9 D of accommodation).[148]

In addition to the easier alignment and capture of the measurement due to the technique being non-contact optical methods have the added advantage of resolution (∼0.012 mm) and precision (∼0.01 mm), an order of magnitude better than ultrasound biometry.[101,149,150] Commercially available devices have test-retest 95% limits of agreement typically reaching ±0.04 mm.[142,143] Some optical biometers use a super luminescent diode light source (rather than a laser diode), improving the signal-to-noise ratio and thus allowing central corneal thickness, anterior chamber depth, and lens thickness to be measured at the same level of accuracy rather than employing image analysis techniques.[102,151] Some recent commercial optical biometers combine highly accurate and repeatable PCI measurement of axial length with a Scheimpflug camera for assessing anterior eye biometry and a Placido disc corneal topographer.[152–155]

Optical coherence tomography (OCT) is also utilized to measure anterior eye biometry, but was originally developed for cross-sectional imaging of the posterior segment of the eye. Fourier-domain OCT methods provide high resolution cross-sectional and volumetric images of the posterior eye with the ability to precisely resolve individual retinal layers at an imaging depth of a few millimeters.[156] Since the development of Fourier-domain OCT, a number of methods and prototype devices have been developed utilizing a range of different approaches to encompass whole eye OCT imaging and axial length measurements.[157–160] These devices provide rapid high-resolution measures of axial length, with precision comparable to other optical methods of axial length measurements.[161–163] The advantage of this OCT imaging approach is that these devices provide cross-sectional images of the eye's component structures (cornea, crystalline lens, and retina), providing additional biometric measures of central corneal thickness, lens thickness, and anterior chamber depth, thereby allowing measurement alignment and localization of ocular interfaces to be more easily verified (with reference to the cross-sectional B-scan image) than are PCI-based methods.

The non-contact measurements, ease of alignment, and high precision measures possible with optical biometry methods, make them ideal for application to clinical trials in the myopia field. These measurement techniques provide the precision required to detect small magnitude differences and changes in axial length in clinical trials. As outlined, there are currently a number of optical biometry devices commercially available and, from the point of view of the precision of axial length measures, most devices exhibit similar performance. One drawback of optical biometry devices (compared to ultrasound methods) is that difficulties can be encountered in providing reliable measures of axial length if dense cataracts are present,[164] but this issue is rarely encountered in the myopia research field given that the majority of clinical trials enroll young participants with clear ocular media.

3.1.2 Refractive Error Measurement. In young children, interpretation of refractive error is complicated by potential errors in measuring refractive state due to the confounding of this measurement due to the influence that accommodation can have on this measurement. The importance of controlling accommodation becomes apparent when comparing measured refractive state with and without cycloplegia. Analyzing a sample of 6017 right eyes of children aged 4 to 15 years, non-cycloplegic refractions were found to be 0.63 ± 0.65 D more myopic than cycloplegic refractions.[165] Twelker and colleagues found similar differences in infants (0.89 ± 0.66 D).[166] These results indicate that noncycloplegic refractions may overestimate myopia in infants and children; since

cycloplegic refractions are indeed a necessity of any myopia control study which has refractive error as a measurement outcome, most studies determine refractive error as part of their inclusion criteria using cycloplegic autorefraction ($n = 17$ of studies in Table 1), although this aspect of the methodology is not always recorded.

As discussed in section 2.6. either 1% cyclopentolate or 1% tropicamide may be utilized, each with their positives and negatives. On average, one drop of 1% tropicamide produced 0.14 D more myopic refractive error measures than one drop of 1% cyclopentolate.[46] Yazdani and colleagues[167] found a similar amount in a meta-analysis of six studies, with tropicamide refractions 0.175 D more myopic. Mutti and colleagues also found this characteristic (0.20 ± 0.30 D) in a prospective study.[168] As between-participant and between-race differences in the myopic bias of refractions are generally larger than many of the myopic changes reported in myopia control studies,[21,24,94,169] it is imperative that any study assessing a myopia control device employ the same cycloplegic procedures for each measure of refractive error throughout.

The reported impact of cycloplegic agents on distance refractive errors reflect well documented differences between participants in drug efficacy.[170] Specifically, dark irises are typically associated with reduced drug efficacy.[45,171] Also, because the time course of cycloplegia and mydriasis can differ,[45,171] pupil size should not be used as an indicator of cycloplegia. It is recommended that clinical trials employing cycloplegic refractions ensure that refractions are performed at a fixed time after drug instillation (e.g., 30 or 60 minutes) and that accommodative status is assessed prior to refractive error measurements being taken. Tropicamide has been reported to have a maximal cycloplegic effect at 30 minutes, whereas the maximal cycloplegic effect of cyclopentolate is reported to be 60 minutes. Given a faster maximal effect and similar reported cycloplegic effect—despite the possibly increased cycloplegia of 1% cyclopentolate—most myopia control studies have utilized 1% tropicamide to obtain their cycloplegic refractions,[21,24] whereas others have used both 1% tropicamide and 1% cyclopentolate.[172]

Although autorefractors still may have repeatability of ~±0.21 D,[173] which could encompass a good percentage of the roughly 0.30 to 0.50 D per-year treatment effect[24,94,169] being targeted, autorefractors typically exhibit higher precision than do participantive refractions (smaller coefficient of repeatability)[174] and minimize unconscious investigator bias. Because of these aspects, only objective refractions should be used in myopia control studies. Furthermore, to minimize variability due to residual accommodation and instrument myopia, autorefractors should be open-field. To assure they provide an accurate measure, they should be validated across their measurement range.[175–177] Since myopia control studies often involve multiple comparisons across several years, instrument stability is essential across the entire duration of the study. If possible, this can be accomplished by initial and continued instrument calibration at specified time frequencies during data collection according to the instrument manufacturers' recommendations. Specially designed model eyes can be used for calibration.[178,179]

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. However, due to ocular aberrations, refractive state can vary significantly across the pupil.[180] Therefore, refraction methods that employ a known pupil location, repeatable across time, are preferred. For example, eccentric photorefraction and retinoscopy can have their results affected by aberrations in the pupil margins,[181,182] while participantive refractions are biased toward the pupil center.[183] Objective methods that employ a known measurement aperture that can be repeatedly located in (or close to) the pupil center are recommended.

3.2 Secondary Outcomes

3.2.1 Patient Reported Outcomes. Most myopia control clinical trials include primary outcome measures that can be objectively measured (such as an autorefractor measure of refractive state or biometric measures of axial length; see section 3.1). However, there are significant insights to be gained from the child's wearing experience, effectiveness of the treatment and understanding the results obtained, by simultaneously capturing child (participant) or parent-reported outcomes. Many measures are common to those of typical contact lens trials, such as assessing comfort, lens awareness, ease of care, wear time and frequency of problems.[184,185] As myopia control strategies often employ multi-zone optics that may create ghosting or doubling of images,[186–188] other informative patient-reported outcomes may include visual quality[189] while performing different tasks (such as reading, computer use, and night vision) and the time to perform these tasks.[184,185] Any participants enrolled in a clinical trial who discontinue treatment should be queried about the reason for the discontinuation.

In clinical trials, the reliability of compliance aspects could be assessed by asking both child and parent/caregiver separately. The agreement between child and parental/caregiver responses is not known, especially as it relates to contact lens use (such as hours of use) and satisfaction. However, results of behavioral research suggest a low degree of agreement, and differential levels of agreement believed to be associated with transitions in age.[190] It appears that agreement between parent and child responses varies with parent experience. Specifically, in a meta-analysis of 19 studies (including health-related quality-of-life instruments), parents with the condition being studied underestimate the child's responses, whereas those without the condition reported higher quality of life than did the child.[191] This result may depend on the specific questions or health-related quality-of-life instrument. Until more information is available, querying both child and parent/caregivers is recommended, as each group will provide valuable information (such as how often a parent has to assist with insertion of a contact lens).

3.2.2 Assessing Treatment Compliance. It is widely accepted that compliance with treatment is an important aspect contributing to the outcome and validity of results in any clinical trial.[192,193] In general, compliance in clinical studies relates to the adherence with the prescribed regimen (such as contact lens wear in a myopia control study investigating the impact of OK). However, there are many other aspects of compliance, including study visit compliance, adhering to study procedures, and reporting adverse events.

Literature relating to the impact of compliance on myopia control clinical trials is sparse. Comparisons can be made with clinical trials in the medical field, where it is known that non-compliance may be underestimated.[194] Assessment of compliance is affected by how it is measured. For example, a clinical study involving an anti-depressant drug estimated a compliance rate of 70% based on evidence of medication in blood samples drawn from the participants, as compared to 92% using pill count as the measure of compliance.[195] It has been estimated that up to 30% of clinical trial participants are untruthful about medication compliance and may be throwing away investigational product prior to study visits.[196,197] This is relevant to pharmaceutical studies as well as studies involving contact lenses, in which compliance can be assessed by the number of lenses used during a specific time period. Participants could be required to bring all unused product to each appointment so

the number of remaining lenses can be counted and compliance based on that count; however, this relies on compliance with replacement frequency and that no product is discarded due to damage. It has also been noted that compliance in clinical studies is generally better in the first few months of a study and drops off thereafter to a level similar to compliance in clinical practice. For example, in a study on children with mild asthma, adherence to the medication dosage prescribed in the clinical study was 75% at the 3-month time point but dropped to 53% after 9 months.[198]

The most common approach to reporting compliance with prescribed practices (such as taking medication or using a device on a regular basis) is to collect data retrospectively on participant activity at the scheduled study visits. This may result in an inaccurate estimation of information from the participant or parent, leading to incorrect data, or data that has to be excluded because the reported information could not be assumed accurate.[199] Participants may not provide accurate reporting of behavioral information, especially when being asked to recall from a considerable time period prior to the study visit.[200] Participants who understand the importance of compliance may choose to modify responses or behaviors to appear compliant.

In an attempt to minimize errors due to recall, a simple method of collecting data on activities outside the study visits is often achieved by means of a questionnaire/diary (such as nightly or weekly between study visits). There is strong evidence to support the use of modern technology (electronic methods) to collect such data. Stone and colleagues reported that despite participants reporting 90% adherence with that written in their paper diaries, the actual rate was as low as 11%. In switching to an electronic diary, the participants are aware that the information is date and time stamped, increasing adherence to 94% and reducing the risk of participants exaggerating their adherence to study protocols.[201] Myopia control studies are typically lengthy, lasting for several years, with a significant time period between appointments. In studies involving contact lenses, participants are generally required to wear lenses for a minimum amount of time and are often required to self-report their wearing schedule (hours per day and days per week). This can be undertaken at periodic intervals between study visits or can be self-reported at each study visit. Reminders to participants, for example, to complete diaries about activities or to ensure that they wear their device for a certain number of hours or days per week, should promote compliance with study protocols.

In the healthcare field, one simple method of electronic reporting is possible through text messaging (SMS) participants. SMS has been found to be both cost effective and beneficial, with the effectiveness of electronic reminders on compliance with medical treatment being well documented. Specifically, Lester and colleagues demonstrated an improvement in HIV treatment outcomes with patients who received SMS support, and Miloh and colleagues[203] demonstrated significant medication adherence and a reduction in rejection episodes when text messaging reminders were sent for pediatric recipients of liver transplants. A systematic literature review by Vervloet et al.[204] confirmed evidence for short-term effectiveness of SMS electronic reminders, but the long-term effect remains unclear.[202–204] Specifically related to optometric clinical trials, Morgan reported up to 93% of participants responding within a 30-minute period of a specified time point using SMS messaging, and Woods and colleagues demonstrated a 97.5% response rate to requests for data from participants generated via smartphone.[205,206]

Gamification is defined as the process of adding games or game-like elements to something (such as tasks) to encourage participation.[207] Gamification within the healthcare field is increasing in popularity and has a positive influence on health behaviors.[208–210] Gamification has been explored as an option for increasing recruitment, retention, and compliance in clinical trials. Rowbotham and colleagues[211] demonstrated that interactive media improved comprehension of research study procedures and risks. Gamification provides a process of rewarding participants for completing tasks, for example, diary completion. Virtual rewards take the form of points or levels and helps drive competitive behavior. In one study using gamification technology, medication adherence increased from 58% to 95%.[212] In a clinical trial setting, gamification could improve compliance, resulting in more robust data.

The emergence of wearable technology into the clinical research space is changing the way in which clinical data can be obtained. Health and wellness devices are commonly worn and are a widely accepted accessory. In 2013, there were over 97,000 mobile health apps available to consumers.[213] By 2017, this number increased to 325,000 apps. It has been estimated that by 2020, there will be 4 million patients using remote monitoring health technology.[214] For the purposes of myopia control studies, information that can be captured by wearable technology includes aspects such as time exposed to certain light levels/spectrums, working distances, and physical activity. There are several examples in the literature of wearable technology being used to monitor light levels, and data obtained from such devices can support assessment of treatment compliance in studies where treatment relates to time spent outside.[215,216]

Participant recruitment and retention are critical to the success of clinical trials and to the validity of the results. Participants are generally required to undergo more clinical procedures than they would in a non-research setting, such as being required to complete questionnaires and attend more frequent appointments. It is important from the outset that the participant—and in many cases the parent/guardian—understands what is required of them for the period of the study. An understanding of expectations will likely result in better compliance with the study protocol and better retention of participants. Where possible, clinical trials should be as participant-centered as possible, for example, ensuring that appointment times are convenient for participants. In the case of studies with children, having appointments available after school hours or on weekends may be necessary.[217,218]

Consent forms (or parental permission forms and child assent forms) that are provided ahead of enrollment should be simple and written in language that participants can understand since there needs to be an appreciation of expectations of compliance to study protocol and what would constitute non-compliance, along with the importance of reporting non-compliance. It is recommended that informed consent documents read by adults be written at or below Grade 8 level.[219] Adults typically read three to five levels lower than the school grade level they completed.[220,221] When children are recruited into clinical studies, an "assent form" is used for the child, and it is imperative that the assent be written in language appropriate for the age of recruitment. Participants with a poorer reading grade level than the level of text in the informed consent form may not understand all of the content of the document.[222] During the recruitment (and follow-up visits), it is important that the participant trusts the researcher, understands that reporting non-compliance is a vital part of study data collection, and that this does not reflect poorly on the participant. Study participants may not want to let the researcher know that they have been non-compliant, as this may "disappoint" the researcher or result in them being withdrawn from the study.

Investigative Ophthalmology & Visual Science

3.3 Exploratory Outcomes

While axial length and refractive error are well established as primary outcome measures of myopia control trials, an increasing number of exploratory outcomes have been adopted to aid in the prediction of efficacy for individuals, to better understand the mechanism of control, or to investigate safety aspects. These exploratory outcomes may sometimes be specific to testing different hypotheses associated with different myopia control approaches: peripheral refraction, accommodative changes, ocular alignment, and posterior segment imaging to optical myopia control techniques; accommodative changes and pupil size to current pharmaceutical approaches; outdoor activities to myopia control environmental policies; and anterior segment imaging and tissue biomechanics to OK.

3.3.1 Peripheral Refraction. In 1801, Thomas Young[223] estimated the astigmatic image shells in a model of his own eye. Hoogerheide and colleagues[224] suggested that certain patterns of peripheral refraction—involving the peripheral retina being less myopic or more hyperopic than the central retina—could predispose an eye to development of myopia. Several studies on different animal models have since shown that image quality on the peripheral retina can regulate ocular growth in chickens,[113,115] monkeys,[225–229] and guinea pigs[120] and that an eye with peripheral hyperopia continues to grow even though the central image is well-focused on the fovea.[229] The review by Wallman and Winawer[230] has inspired many investigations of human peripheral refraction, and the interest in refraction has extended to include higher-order aberrations. Relative peripheral refraction is a surrogate for eye shape, but it does not describe the optical experience thought to regulate eye growth.

As described earlier for central (foveal) refraction, the peripheral refraction is preferably measured with accommodations paralyzed to avoid changes in the optical profile (see review by Lundström and Rosén[231]). Furthermore, it is practical to express peripheral refractions in terms of mean sphere and two astigmatic components[232]:

$$M = S + C/2$$

$$J_{180} = -(C/2)\cos(2\alpha)$$

$$J_{45} = -(C/2)\sin(2\alpha)$$

with S/C × α being the sphere/cylinder/axis format. In the M, J_{180}, J_{45} format, statistical analysis is easy to perform and at any appropriate time conversion can be reverted back to S/C × α format. As well as absolute values, relative peripheral refraction is often specified in which central M is subtracted from peripheral refraction M values.

Studies of the peripheral refraction in human eyes have shown a consistent difference at the group level between eyes of different central refractive states; myopic eyes tend to have a more hyperopic relative peripheral refraction (typically around +1.00 D in the 30° temporal visual field) than do emmetropic and hyperopic eyes (typically between 0 and −1.00 D), but the variation between individuals can be large.[231] These differences may be largely a consequence of the excessive eye growth, causing myopic eyes to be more elongated relative to emmetropic eyes,[106] and the hypothesis that peripheral refraction of the uncorrected eye may be used to predict which children might develop myopia[224] has not been supported in clinical studies.[233–236]

It is difficult to give criteria for differences or changes in peripheral refraction pattern that could be considered clinically significant. To the best of our knowledge, no such criteria have been suggested. Several studies have made group or treatment comparisons at individual field locations, mostly along the horizontal visual field and at angles from ±10° to ±40°. Note that relative effects will be more pronounced as one moves further from fixation. Values have high interparticipant variation in the region of 15° into the temporal field, corresponding to the optic disk on the retina; these are usually discounted in analysis. A related issue is how far from fixation that peripheral refraction would be considered relevant to development and progression of myopia; in this regard, Mathur and Atchison[237] suggested an outer horizontal meridian limit of 40° from fixation as beyond that angle many adult emmetropes had a pattern of relative peripheral hyperopia. A relevant angle could be 30° in the temporal visual field, in which myopic and emmetropic eyes tend to be separated by less than 2.00 D, as mentioned above. Therefore, 2.00 D would set the upper limit for a criterion on differences in relative peripheral refraction of practical significance. The lower limit for a criterion could be set by depth-of-field, which increases with eccentricity as both astigmatism and higher-order aberrations increase in magnitude off-axis[231]; at 30° temporal visual field astigmatism gives a Sturm's interval of around 1.00 to 2.00 D. In this context, it should also be noted that the most common design of optical corrections for myopia prevention cause further increases in the depth of field.[238] With this reasoning, a criterion on differences in relative peripheral refraction of practical significance at 30° temporal visual field could be in the order of 0.50 to 1.00 D. However, it may be more relevant to the emmetropization process to compare different peripheral field meridians with each other instead of with the fovea, such as asymmetries between the temporal and the nasal visual fields.[239,240]

In addition to uncorrected peripheral refraction, there is also interest in measuring corrected peripheral refraction (peripheral defocus) after OK and while wearing a contact lens. Myopic peripheral defocus has been hypothesized to slow myopia progression. Although relative peripheral refraction of the uncorrected eye may not be associated with myopia onset or progression (see previous), some longitudinal studies have reported an association between peripheral refraction while wearing correction and myopia progression.[94,241] Standard spectacles can increase peripheral hyperopic defocus,[37,39,242] while multifocal spectacles and contact lenses can cause myopic peripheral defocus.[241,243,244] The use of autorefraction to determine the effect of a particular optical device on peripheral defocus may be of interest as a secondary outcome in studies trying to determine factors that may predict which eyes respond best to a myopia control lens design. Standardized measurement methods are needed in such studies.

Peripheral refraction has been determined by several methods, including variations of participantive refraction, retinoscopy, manual optometers (such as the Zeiss coincidence and parallax optometers), the double-pass point-spread function, photorefractors, autorefractors, and aberrometers.[231,245] Participantive refraction is challenging because of reduced retinal function making judgments difficult, so there are few reports.[237,246–248] Retinoscopy, which has been used since the late 19th century,[249] requires considerable examiner skill and is not as repeatable as autorefraction.[250]

In applications of these techniques, the eye is often rotated to align the measurement axis of the instrument with the desired visual field location. It is common to set up external fixation targets along the horizontal visual field for open-field autorefractors. However, a large eye rotation will alter muscular stress as well as eyelid pressure on the eyeball, potentially causing optical changes,[251–253] although such

changes have not been noted in more recent studies.[254–256] In the case of contact lenses, it should also be noted that El-Nimri and Walline[257] found that eye movements can cause shifts in soft contact lenses by more than 0.5 mm, and thus have the potential to affect peripheral refraction measurements. It is recommended that (where possible and without slowing measurement time) eye movements should be limited during peripheral refraction testing, especially when measuring at large angles.

The main instruments used to determine refraction in the peripheral visual field in the last 15 years are commercial open-field autorefractors, mainly Shin-Nippon (Osaka, Japan), Grand Seiko instruments (Mahwah, NJ, USA), and Hartmann-Shack wavefront sensors (such as Thorlab, Inc., Newton, NJ, USA), while the latter can also be used to determine higher-order aberrations. A few laboratories have developed "automated" instruments to shorten measurement time.[258–260] There are issues associated with each type of instrument for peripheral measurement, for which they were not designed:

3.3.1.1 Autorefractors. The Shin-Nippon and Grand-Seiko instruments record refraction corresponding to an annulus in the pupil of 2.3 to 3.0 mm[177]; imprecise positioning over refractive corrections with narrow optical zones could lead to erroneous measurements, although consistency has been demonstrated with accurate placement.[261] When there are rapid changes in the optics across the field, the measured refraction does not keep pace. The extreme case is when there is a discrete change in the optics, such as occurs with concentric bifocal intraocular lenses and contact lenses (a central zone is responsible for distance vision and a peripheral zone is responsible for near vision, or vice versa). Other examples are when corneal shape is altered by refractive surgery[262,263] or OK.[264,265,266] As long as it is understood that there is a lag in refraction changes into the periphery, this is not a major concern. When planning clinical trials, it is also important to recognize that repeatability of autorefraction declines when further measurements are made in the periphery in both normal eyes[173] and in eyes that have undergone OK.[172]

The majority of peripheral refraction measurements with the instruments have been along the horizontal meridian, with few measurements along the vertical meridian[239,267] and only one study has considered oblique meridians.[268] Osuagwu and colleagues[269] found that higher-order aberrations, such as coma, affect the shape of the retina image for oblique meridians, consequently affecting refraction measurement along these meridians. While this was investigated with the Shin-Nippon/Grand Seiko SRW-5000 with an analyzing pupil annulus of 3.0 mm diameter, and may be of less consequence with newer versions such the Shin-Nippon NVision K-5001/Grand Seiko WR-5100K with a smaller 2.3 mm analyzing pupil, the authors recommended that autorefractors should not be used to determine peripheral refraction along oblique meridians and advised that instruments be validated before being used outside the scope intended by the manufacturer.

3.3.1.2 Wavefront Sensors. The size and shape of the pupil used in analysis is important. The pupil is mostly circular on-axis, but when viewed off-axis, it becomes elliptical in shape, making traditional methods of power determination utilizing a Zernike fitting problematic.[237] Alternatives in dealing with this approach and using a Zernike fit include using an elliptical pupil shape stretched along its minor axis to become a circle, or using a circular pupil whose diameter matches either the larger or smaller dimensions of the elliptical pupil. These different approaches will give different errors and estimations of aberrations. Aberrations, although with correct manipulation, they will give similar estimates of refraction from even-order Zernike aberration coefficients. Comparison and conversion code for the different estimations were given by Lundström, Gustafsson, and Unsbo.[240] Based on simplicity of approach, possible departures of off-axis pupils from ellipticity and ease of understanding, a circular pupil approach based on a diameter that fits within the actual pupil should be adopted.[231,270] Alternatively, as this approach may bias the results to the central optics—of possible importance when measuring through center-surround zonal lenses—Zernike fitting could be avoided all together by either determining refractive power based on the local slope/zonal integration[271] or by calculating the wavefront vergence based on the raw slope measured by the instrument.[272]

Charman and colleagues[270] argued that visual field (such as superior visual field) rather than a retinal (such as inferior retina) reference be used when describing peripheral refraction measures. Specifically, the angles associated with each measure and distances from fixation should be specified in terms of object space rather than within the eye. For sign convention, most peripheral refraction studies have assigned positive values to the nasal visual field and the superior visual field.[231] It has been suggested that the ophthalmic optics convention of determining visual field meridian in terms of an anticlockwise angle (from the right side when viewing a patient's eye) be adopted, in which case the eccentricity does not require a sign.[270]

Peripheral aberration coefficients across the visual field show considerable mirror symmetry between right and left eyes.[269,273] In a pooled data set (such as when combining temporal visual data of right and left eyes and combining nasal visual data of right and left eyes), the coefficients with negative correlations between right and left eyes require sign changes for left eyes. The correction needed is that used for positions in the pupil for on-axis aberrations as specified in the ISO standard for ophthalmic wave aberrations.[274] Specifically, signs of left eye coefficients are altered for which the Zernike polynomial functions Z_n^m (m = radial degree and n = azimuthal degree) have negative, even m-indices or positive, odd m-indices, such as for C_2^{-2}, C_3^1, C_3^3, C_4^{-4}, and C_4^{-2} (the coefficients for oblique astigmatism, coma, trefoil, and oblique secondary astigmatism, respectively).

Another consideration is the same issue described above relating to autorefractors regarding the effect of rapid spatial changes in the optics during refraction measurements. In the case of "regular" changes such as OK, the analysis pupil size can be varied to more clearly show changes in refraction; for example, analyzing with a 2-mm pupil rather than a 3-mm pupil will show more rapid changes and better reflect changes in corneal surface shape. However, there will be problems with discrete changes. Figures 2 and 3 show spot diagrams and wave aberration maps for a theoretical example of a distance-center bifocal lens combined with a model eye, in which the center and peripheral contact lens zones contribute in varying amounts to imaging and the determination of aberrations as the horizontal visual field angle changes. How a particular instrument deals with this depends on its sampling density, its algorithms for determining transverse aberrations, and Zernike wave aberration fitting. Clearly, there is no oblique astigmatism here, but one paper has reported considerable, artifactual, oblique astigmatism (J_{45}) for a distance-center lens rising to ≈0.70 D at about 25° horizontally from the center of the field.[275] The problem is the inadequacy of fitting Zernike aberration polynomials with these lenses with multiple or discrete zones. A partial solution for measuring refractions through such lenses is to determine refractions from Zernike circular polynomials obtained using small pupils (such as 1 mm) and ignore discontinuities corresponding to zone boundaries. Alternatively, more elaborated image quality

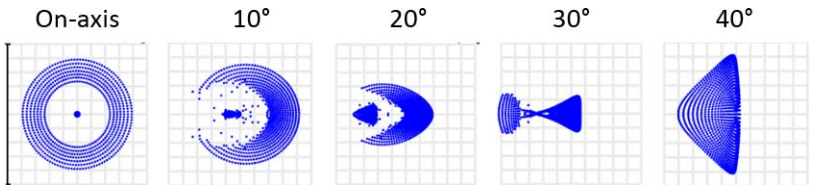

FIGURE 2. Spot diagrams for a distance-center bifocal contact lens combined with the Navarro schematic eye,[276] as a function of horizontal visual field angle. Out of the eye raytracing, distance power 0D, addition +2D, center zone diameter 2 mm, refractive index 1.43, pupil size 3 mm, back surface of contact lens is that of the cornea at 7.72 mm. Drawn with Zemax OpticStudio 16.5 SP1 (Zemax, LLC, Kirkland, WA, USA).

metrics than those calculated directly from the Zernike coefficients could be used when analyzing the peripheral optical effect of these lenses. Rosén and colleagues[238] used the area under the MTF curve for a 4-mm pupil diameter, which provides a more complete description of retinal image quality, reflecting the ambiguity of defining the far point with a discrete change in refraction over the pupil. Additionally, as described, refractive power could be obtained based on calculations from the local slope/zonal integration[271] or by calculating the wavefront vergence based on the raw slope measured by the instrument.[272]

3.3.2 Accommodation Changes With Optical Devices.

3.3.2.1 Lag of Accommodation. Accommodation lag is usually measured participantively with MEM or Nott retinoscopy, or objectively[277] with an open-field autorefractor[81,278–281] or wavefront aberrometer,[282] with the participant viewing through their distance correction (or spherical equivalent lenses). The lag of accommodation is calculated as the change in measured refraction from distance viewing subtracted from the anticipated accommodative demand related to the target distance.[28,282] If the measurement of accommodative response is derived from aberrations over a particular pupil size, then, for the measurements to be accurate, the change in the individual's eye focus should be weighted to their dynamic pupil changes.[283] To fully drive the accommodative system, the target should be high contrast and close to the maximal visual acuity threshold.[284] Alternatives include using fused cross-cylinders,[86] monocular estimate method,[285] and Nott retinoscopy, all of which are less accurate and repeatable.[277]

3.3.2.2 Dynamic Changes of Accommodation. Accommodation is a dynamic process and allows pre-presbyopes to focus across a range of distances. Dynamic changes of accommodation can be measured with open-field autorefractors (including photoretinscopy)[286–288] and aberrometers,[289] but this has not been adopted in current myopia control studies. However, dynamics of accommodation will affect the peripheral retinal image focus, which could impact on the treatment effect if based on the peripheral refraction hypothesis.

3.3.3 Ocular Alignment. While most bifocal or progressive multifocal spectacle studies have reported only minimal reductions in myopia progression, larger reductions in progression have been reported in children with nearpoint esophoria or accommodative dysfunctions.[96,290] Multifocal contact lenses worn by children can induce exophoria, increasing with accommodative demand.[79] OK causes minimal effects on ocular alignment,[291] and a link between OK or pharmacological treatments for myopia control has not been reported. These results indicate some potential benefit of monitoring heterophoria either upon inclusion in a study or during the course of the study.

Heterophoria has been assessed in myopia control treatment evaluations in a variety of ways, including alternating cover test,[21,280,292,293] Howell-Dwyer near phoria card,[33,294,295] Maddox wing/rod,[293,296] prism dissociation,[81] and von Graefe and modified Thorington techniques.[79,83,297]

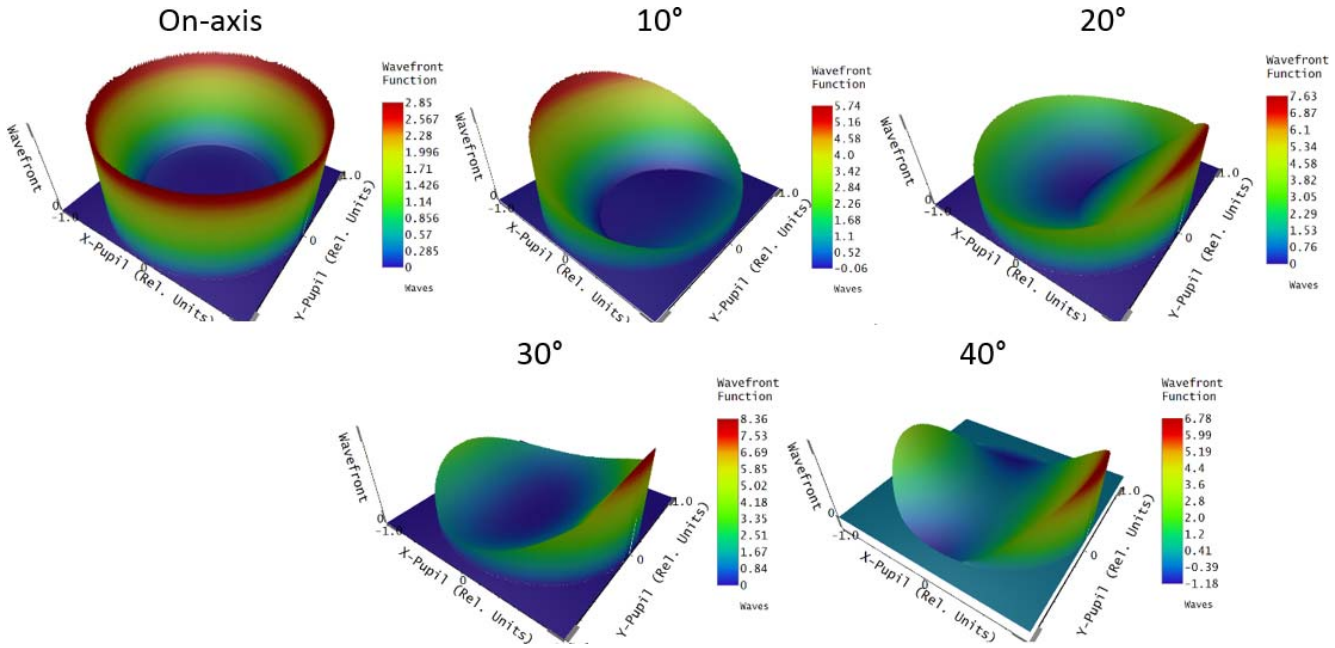

FIGURE 3. Wave aberration maps in the exit pupil plane for a distance-center bifocal contact lens combined with the Navarro schematic eye. Conditions are the same as for Figure 2. Drawn with Zemax OpticStudio 16.5 SP1 (Zemax, LLC).

Different free-space heterophoria measuring techniques do not give equivalent values.[298] The modified Thorington technique (a tangent scale technique for assessing dissociated phoria) has been shown to be the most repeatable of the established techniques for phoria assessment, with good inter- and intra-examiner reliability.[298,299]

3.3.4 Pupil Size. Pupillometry is a critical measure in most myopia clinical trials due to the limitation of the pupils on the transfer of the effects of optical interventions onto the retina,[300] or to assess the adverse muscarinic receptor effect of myopia control drugs.[82] Pupil size is also critical in modeling ocular aberrations (see "Clinical Trial Outcomes and Related Instrumentation: Primary Outcomes"). Pupil size can be estimated participantively and its dynamics checked with a light source[82] but is better measured objectively using dedicated pupillometers,[30,47,301,302] some biometers[303] or aberrometers/topographers.[304] Pupil size varies with task and light levels, so it is complicated to analyze and report. However, measurements are not often reported.

3.3.5 Outdoor Activity/Light Levels. The rapid increase in myopia prevalence seen over the last few decades[305] implicates a change in the environment as the primary causal agent for the current global myopia epidemic. However, the obvious geographic and racial differences in reported myopia prevalence and severity (such as very high prevalence, early onset, and high levels in East Asia), and the familial clustering of myopia[306–309] are consistent with genetics playing a significant role. Increased levels of myopia in racial subgroups within racially mixed societies, such as Australia and Singapore,[310–312] are also consistent with genetics playing a role. The hybrid hypothesis proposes that environmental changes over the last few decades in combination with a genetic susceptibility (those with East Asian genes or with the genetics from myopic parents) have jointly contributed to the current myopia epidemic.[305,313] Sorting out these competing hypotheses is a classic nature-versus-nurture challenge for the research community.

If environmental changes are responsible for elevated levels of myopia, what characteristics of the environment are responsible? Experimental studies on animals support the hypothesis that the retina plays the central role in regulating eye growth (see accompanying IMI – Report on Experimental Models of Emmetropization and Myopia).[314] Also, there is evidence that retina-specific environmental factors contribute to myopia development in humans, such as retinal light exposure of microscopists[315] and retinal deprivation from ptosis/cataract.[316] It is likely, therefore, that changes in the light environment (intensity, spectral content, optical distance) have contributed to this epidemic, rather than non-visual environmental factors such as air pollution and diet (see accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report).[317]

Establishing a causal relationship between environmental factors and myopia development is challenging for several reasons:

1. The significant covariance of many factors potentially involved in myopia development, such as more time outside, will always be negatively correlated with less time inside.
2. Activities are generally different in indoor and outdoor environments. Sporting or other physical activities involving distant visual stimuli are common in the outdoor environment, whereas physically sedentary activities (such as watching TV and reading) combined with near viewing are common in interior environments. It is important to recognize that small differences in near viewing distances can dramatically alter the optical stimulus (target vergence), the accommodative response, and the defocus experienced by the eye.
3. Myopia development is slow (typically <1.0 D per year[128,318]), and refractive measures have coefficients of repeatability of about this magnitude, necessitating multi-year monitoring. On the other hand, measures of axial length have higher precision[149] and can reliably detect smaller changes in myopia progression (such as those occurring over shorter periods of time).
4. Most studies assessing outdoor exposure time have employed survey tools. These questionnaires have ranged from a single question on outdoor activity[319] to more detailed questionnaires estimating time engaged in a range of leisure and sporting outdoor activities on weekdays and weekends as utilized in the Sydney Myopia study[320]; however, accurate measures of the multidimensional properties of the visual environmental experienced by children are difficult to infer from these survey tools[321] since they cannot quantify key parameters such as light level or viewing distance and are participant to recall bias.[322] Studies have noted that there is generally poor agreement between outdoor exposure time derived from questionnaires and outdoor time derived from objective measures of outdoor light exposure.[216,323]
5. Standard corrections for myopia (such as single vision spectacle or contact lens corrections) may also alter retinal experience. This has also raised the question of whether traditional myopia treatments somehow contribute to the myopia progression of control groups in a clinical trial.[324]
6. Modern techniques have been able to quantify personal environmental light levels using wearable photodetectors[216,325] and physical activity levels using accelerometers,[325,326] providing the ability to give objective measures of outdoor exposure times in children. However, characteristics of the light environment determining the retinal image characteristics have not been specifically quantified. For example, because of the brow, the eye generally does not experience direct solar irradiation, whereas a light detector mounted on clothes can be directly illuminated by the sun. Will body-mounted light monitoring systems accurately reflect the true retinal illumination?

Some recent studies examining the relationship between myopia and outdoor activities have employed a range of different objective devices to estimate outdoor exposure, including wearable light sensors affixed to clothing (such as HOBO Pendant light loggers; Microdaq.com Ltd, USA)[216,323,327] and wristwatch sensors that combine light sensors and measures of physical activity (such as Actiwatch devices; Philips Respironics, Andover, MA, USA)[325,328,329] and the recently developed FitSight fitness tracker (Singapore Eye Research Institute, Singapore).[215] These wearable sensors provide detailed objective assessments of light exposure patterns. Through continuous measures of light exposure, and current device battery life and data storage capacity, the devices can be worn for up to a month (recharging devices and the ability to wirelessly synchronize data to other smart devices should allow longer measurement periods). The majority of studies employing wearable light sensors to provide objective measures of outdoor exposure time have utilized a light intensity cutoff value of >1000 lux to delineate between outdoor and indoor exposure, since light levels >1000 lux are not commonly experienced when indoors.[215,216,323,325,328] A recent study comparing light exposure measures (collected with a wristwatch light sensor) derived from a range of sampling frequencies and durations has recommended that for

the most reliable measures of outdoor light exposure in children and adults, light exposure measures should be collected for at least a week with measurements sampled at least every 2 minutes.[330] Recent technological advances also enable accurate monitoring of real-time viewing distances, to allow the dioptric mapping of the visual environment, which helps reveal any potential relationship between chronic viewing distances and myopia development.[329,331–333]

Finally, although the preponderance of evidence supports the idea that increased outdoor activities and, by necessity, decreased indoor time, are associated with lower levels of myopia,[320,322] most of these studies can reveal only an association. A number of recent interventional studies have also shown that interventions to increase children's daily outdoor exposure time have resulted in significant reductions in myopia development compared to control groups.[334–336] Of course, there are some potentially confounding causal relationships (such as hyperopic children are less likely to read because of the increased accommodative demands and possible fusional failures that can result).[337] Are these children more likely to spend time outside because of their refractive state and not vice versa? Further, because many outdoor activities require distance vision (such as playing cricket and baseball), children with myopia may be less inclined to participate in outdoor activities, again suggesting that it could be the refractive state causing the environmental differences and not the other way around.

If myopia levels and progression are dominated by the refractive state at the start of a study, then environmental experiences prior to the emergence of myopia may be the causal agent,[338] which is consistent with the key conclusion of Xiong and colleagues,[322] that outdoor activity can protect against the onset of myopia but not its progression. These results suggest that environmental studies of children prior to the ages typically associated with myopia onset might be required to reveal environmental factors responsible for myopia onset. Another issue may be reliance on inaccurate measures of time spent outdoors,[321] inadequate number of data samples,[339] and body-mounted light dosimeters that might misrepresent the amount of light in the retinal image.[340]

Because outdoor activities are often very different from those practiced indoors, activity becomes a significant covariable for environmental light levels. For example, in studies that did not directly measure physical activity,[341] the significant association between emerging myopia and outdoor sports cannot be separated from the light exposure covariable. Studies that surveyed activities as well as time outside[320] made tentative conclusions that it was more outdoor time and not sporting activities that were responsible for lower myopia rates in children. More recent studies that actually measured physical activity[328,342] failed to find any association between physical activity and myopia development.

Given the impact of light exposure and outdoor activities upon eye growth, there is potential for differences in outdoor exposure to interact with treatment effects in clinical myopia control trials. Clearly, the collection of detailed data to estimate outdoor time or light exposure in treatment and control populations is imperative for clinical myopia control trials involving interventions. In addition, during myopia clinical trials of optical devices or pharmacological agents, the season in which the study is commenced and measurements are collected should be at consistent times of the year for each child in a multi-year study. Nonetheless, measures at other time points throughout the year may be beneficial in supplementing annual measures since it is likely that enrollment in longitudinal clinical trials will stretch across multiple seasons.

3.3.6 Anterior Segment Imaging. Scheimpflug imaging and Optical Coherence Tomography (OCT) have been extensively utilized to examine differences in the anterior chamber with refractive error, although they are not generally used to assess myopia control techniques. Longer axial length is associated with a flatter corneal curvature, decreased corneal thickness and decreased endothelial density.[343–346] Some studies have found that eyes with high myopia have thinner corneas than eyes with emmetropia or other refractive errors,[347] whereas other studies showed no relationship between refractive error and corneal thickness.[348] Anterior chamber depth has been found to be deeper in myopic eyes,[346,347,349,350] creating an increase in anterior chamber volume.[351–353]

Several studies have reported the ciliary muscle, as imaged by OCT, to be thicker in myopic than in emmetropic eyes,[354–358] whereas others have not found a significant effect of a longer axial length on ciliary muscle thickness.[359] Ciliary muscle thickness has been shown to be thicker temporally than nasally with an association with refractive error in humans.[359] Ciliary muscle ring diameter increases (by 0.10 mm/D), the anterior lens surface steepens (by 0.011 mm/D),[360] and crystalline lens depth from the anterior chamber decreases[352] with increasing myopia. Changes in the anterior chamber depth with accommodation are significantly less pronounced in eyes with high myopia than in emmetropic eyes, but in some myopic eyes accommodation caused the anterior chamber to become critically shallow.[361]

Studies utilizing Scheimpflug imaging have shown that OK lens wear alters the anterior corneal shape rather than the posterior corneal shape and the anterior chamber depth,[362,363] although one study noted a slight flattening of the posterior corneal surface over 1 year.[364] However, Chen et al.[365] observed that steepening of the posterior cornea was observed immediately after lens removal, and it returned to its original shape within 2 hours after cessation of lens wear. Anterior segment biometric depths do not appear to change over either short-term (6 months)[366] or long-term (2 years)[367] OK, although axial length increases significantly. High resolution Scheimpflug imaging can calculate corneal power from its shape profile and, using this technique, has demonstrated that axial elongation over time is slower with greater OK-induced changes in refractive power between the central to the mid-peripheral cornea.[368]

3.3.7 Posterior Segment Imaging. Since changes in posterior eye structures (such as the retina, choroid, and the optic nerve head) are known to accompany myopia,[121,124,126,369–371] imaging of posterior segment structures and the assessment of quantitative changes in posterior eye tissues are useful adjuncts to measures of refraction and axial length in myopia clinical trials. These measures provide insights into the mechanisms underlying observed refractive and eye length changes, and they contribute toward understanding the association between myopia and the development of posterior segment ocular pathology.[372] While there is a variety of instruments available for the assessment of the posterior segment (such as ultrasound), the ability of Fourier-domain OCT to provide non-invasive, high-resolution posterior segment images allowing quantitative measures of both the retina (and individual retinal layers), choroid, and optic nerve, makes this an ideal technology for assessing posterior segment ocular structures in myopia research.

Standard OCT imaging methods were designed to optimize retinal imaging; therefore, studies to quantify choroidal parameters should employ additional methods to optimize the image of the choroid and visibility of the chorio-scleral interface.[373] Imaging techniques such as B-scan frame averaging and enhanced depth imaging are available on a number of commercial OCT devices for improving imaging of the choroid, and OCT's with longer wavelength light sources (for example,

1050 nm) also provide enhanced visibility of the choroid.[374] A number of factors can influence the reliability of quantitative retinal, choroidal, and optic nerve measures from OCT images, such as the density of B-scans used to sample a retinal region, the registration of scan locations (within and between participants), magnification factors associated with differences in refractive error and axial length, refractive index assumptions, and between-participant variations in anatomical factors such as the disc-fovea angle.[375,376] These potential confounding factors should be considered in clinical trials employing OCT imaging to draw the most reliable inferences from data. OCT image segmentation also often requires some manual checking by expert graders (particularly for choroidal measurements). Appropriate masking of image graders is required.

Clinical trials assessing pharmacological or surgical-based myopia control interventions should also include posterior segment imaging to assess the potential for such treatments resulting in any adverse effects to the posterior segment (for example, retinal toxicity). While fundus photography and ophthalmoscopy are typically employed in clinical trials to assess adverse retinal effects associated with pharmacological treatments, additional retinal measures—such as fundus autofluorescence, OCT imaging, and electroretinogram techniques—provide additional structural and functional retinal measures that are useful in the assessment of possible retinal toxicity.[377,378]

3.3.7.1 Retinal Contour Determination. Methods for assessing ocular biometry and imaging the posterior segment can also be used to derive measures of retinal shape.[379] Retinal shape is an important factor influencing peripheral refraction.[373] Retinal shape has been considered for emmetropic versus myopic eyes, in different races, and for retinal asymmetry. In the future, it could be used to monitor the effects of treatments as something more sophisticated than determining changes in axial length. Retinal shape has been determined by several methods, including X-ray radiography, ultrasonography, computerized X-ray tomography, partial coherence tomography, OCT, and magnetic resonance imaging (MRI).[380]

A direct way of determining retinal shape is with the use of MRI, which is not affected by imaging through the eye but has low resolution on the order of 0.25 mm in-plane.[381] A number of factors determine resolution, including the types and configuration of the radio-frequency coils used to transmit and receive the radio-frequency pulses, the imaging pulse sequences employed, and whether 2-dimensional or 3-dimensional data are required. Fine features such as the foveal pit cannot be resolved, meaning that estimations have to be made of the visual axis. It is somewhat impractical for clinical trials due to its testing time, current poor availability, and high expense.

Because of optical distortions, methods such as partial coherence tomography and OCT must be combined with other biometric measurements and with ray tracing based on optical eye models. These methods seem promising in approximating measures of retinal shape obtained from MRI.[379,382] While MRI can yield good eye shape estimates for the majority of retinas, it is probably not that helpful for restricted regions of the retina corresponding to the $\pm 30^{\circ}$ field in which peripheral refraction measurements are usually made[383]; the other methods may be of more value for such restricted regions.

Different estimates of retinal shape have been made. These include ratios of axial length to the horizontal and vertical dimensions (the latter two usually measured from one side of the retina to the other),[106] ellipse or ellipsoidal dimensions giving estimates of surface asphericity,[383,384] type of retinal stretching in myopia (such as global, equatorial, posterior polar, and axial),[380] retinal asymmetry such as comparing retinal distances to a nodal point in different meridians,[381] and inferences of the overall eye shape as being oblate or prolate on the basis of an eye having relative peripheral myopia or relative peripheral hyperopia, respectively.

3.3.8 Tissue Biomechanics.

3.3.8.1 Sclera. Scleral biomechanical changes are known to occur with increasing levels of myopia in the human eye.[385–387] Specifically, axial elongation has been found to be associated with weakened biomechanical properties of the posterior sclera.[388] It is unclear whether these biomechanical changes are a precursor to or a consequence of myopia. It is proposed that an accurate non-invasive assessment of material properties of the sclera in vivo would enable early detection and monitoring of eyes at risk of developing myopia as well as improving our understanding of the mechanism by which these alterations occur.

Non-invasive strategies with potential clinical applications have included: MRI imaging,[389] anterior OCT,[390] indentation tonometry,[391] ocular and fundus pulse amplitudes,[392] ultrasound elastography,[393] assessment of axial length changes following manipulation of external pressure,[394] and internal IOP.[395] Despite such attempts, most of these methodologies are crude and lack the accuracy and sensitivity needed to identify changes in tissues strength between myopic and non-myopic eyes.[396]

With the growing popularity of corneal collagen cross-linking (CXL) for treating keratoconus, there is interest in the application of CXL to the sclera to possibly arrest axial growth.[397] Thus far, scleral CXL has been assessed only in animal models, with early results showing increased biomechanical strength and reduced rate of myopic changes.[398,399] At present, if CXL is applied to the in vivo human sclera due to technical limitations in assessing scleral biomechanics, outcome measures are likely to be limited to biometry and refractive error changes.

3.3.8.2 Cornea. Given that the biomechanical assessment of the in vivo sclera is limited, much of the research relating to myopia and ocular biomechanics concerns the cornea. As both structures are predominantly composed of collagen and have similar embryological origins, it is generally assumed that scleral biomechanical changes may translate into corneal alterations.[400] The validity of this assumption is unclear and there is significant ambiguity in the literature as to whether corneal structural and biomechanical changes occur in myopia.[401–403] Nonetheless, it is widely agreed that corneal biomechanics is important in OK and considered to be a significant outcome measure.[404,405] Indeed, improved understanding of how biomechanics of the anterior ocular surface vary during myopic OK will provide a better understanding of the role of tissue biomechanics in the corneal shape change induced during treatment. Biomechanics can also inform improved lens design for individual patients. Basic structural attributes of the cornea are commonly assessed by pachymetry and topography,[406–408] while techniques such as the corneal deformation to air pressure response provide the means to assess dynamic corneal biomechanics in vivo.[403,405,409,410]

4. Conclusions

This report presents recommendations from International Myopia Institute members on clinical trial protocols and instrumentation to assess the efficacy of myopia control treatments. A general consensus on study design was reached regarding:

- The clinical trial protocol should adhere to the tenets of the Declaration of Helsinki and be approved by the

Table 5. 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

appropriate local ethics committee. Informed consent should be written in a simple language and be acquired from both guardians and children. An adverse event reporting standard should be established. Clinical trials should be registered on a recognized clinical trials registry.

- Minimum length of a clinical trial is 3 years, with year 3 being without treatment (or with only control treatment) to assess any rebound effect.
- Participant inclusion and exclusion criteria should be clearly defined to include age, spherical equivalent refractive error, astigmatism, anisometropia, and ocular pathology. Participants with a history of any previous myopia control treatment should be excluded.
- The included participants should be randomized into one (or several) treatment group(s) and one control group. Stratified randomization is useful to achieve age-matched and level of refractive error-matched groups.
- The control group should receive a treatment that, as far as possible, cannot be distinguished from the active treatment, including the information provided and the ocular health assessment conducted. Common control treatments are single vision spectacles, monofocal soft contact lenses, and a similar vehicle for pharmacological interventions.
- The examiner collecting outcome data should always be masked to the group-belonging of the participant. Masking of the participant should be utilized whenever possible.

The International Myopia Institute strongly recommends using axial length as primary outcome measure of the efficacy of myopia control treatments as well as refractive error when applicable. Axial length should be assessed with an optical biometric method, such as optical partial coherence interferometry that provides non-contact measurements with high accuracy and precision. Refractive errors should be measured objectively under cycloplegia with an open-field autorefractor with a known measurement aperture that can be repeatedly located close to the pupil center. The same type of cycloplegic agent (preferably 1% tropicamide with optical treatments) should be used throughout the clinical trial, and refraction must not be measured before the maximal cycloplegic effect has been achieved (an assessment of depth of cycloplegia should be made before measurement). The refractive errors should be expressed as mean spherical equivalent and astigmatic power errors. To ensure accuracy, the same instrumentation should be used throughout the time period of the clinical trial and must be calibrated and validated using an eye-model. The procedure should be carefully described to allow for easy comparison, replication, and benchmarking. Finally, when stating the reduction in axial elongation and myopia progression between a treatment and a control group, it is critical to report the time period over which the reduction occurred. The meaningful treatment effect over 3 years (2 years treatment + 1 year of no treatment to identify any rebound effect) should be considered on a study-by-study basis on factors identified in section 2.9 (see Fig. 1).

This report also provides an overview of secondary and exploratory outcomes, which could be useful for future instrumentation and treatment development (Table 5):

- Treatment and visit compliance is important for the validity of the conclusion of a clinical trial. Electronic reporting and reminders (e.g., via text messages) have been shown to increase compliance.
- Participantive reporting on comfort and visual quality during treatment is often assessed via questionnaires, preferably electronic. Furthermore, for any participants who discontinue treatment, the reason for discontinuation should be documented.
- Binocular vision, heterophoria, and accommodative function (at a minimum lag of accommodation and consider accommodation facility) correlate with the efficiency of the myopia control treatment and should at least be assessed at baseline of the clinical trial.
- Several different modalities to measure visual function exist. Participantive visual acuity should be determined with logMAR charts. Additionally, contrast sensitivity, reading speed, and glare estimation can provide more detailed knowledge because they are more sensitive to the quality of the retinal image.
- Peripheral refraction may be associated with myopia progression and should be measured using a method such as an open-field autorefractor validated for the purpose. Preferably, head-turn should be used instead of eye-turn. The most susceptible retinal area is not known, but as a starting point it is recommended to assess the optical errors 30° in the temporal visual field and also the corresponding angle in the nasal visual field. Further out in the periphery, measures of retinal shape may also provide estimates of the peripheral refractive errors.
- Outdoor versus indoor activity is also associated with myopia; outdoor activity early in life possibly protects against onset of myopia, but with equivocal evidence for progression. Environmental studies of children prior to the ages typically associated with myopia onset might be required, with new technologies to enable more complete descriptions of the child's visual environment. Furthermore, differences in outdoor exposure may interact with treatment effects, and the protocol of clinical myopia control trials should be designed to account for the influence of seasonal variation on the estimated yearly progression of myopia.
- Give detailed assessments of the ocular biometry; for instance, OCT is of special importance for some myopia treatments. Pharmacological- or surgical-based myopia control interventions should include posterior segment imaging to assess any adverse effects to the posterior segment. In OK, information on the anterior segment,

especially corneal curvature and thickness, is essential, but corneal tissue biomechanics is also important to improve the lens design. Lens position and thickness may also vary prior to and during myopia progression, and an assessment of these at baseline and study end is warranted.

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