Study Title: The Emmetropization Via Accommodation (EVA) Study

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Emmetropization Via Accommodation (EVA) Study

I. Objective. The objective of this study is to determine if wearing a moderate spectacle under-correction (3.00D) and performing activities designed to stimulate accurate accommodation during a 15-month period will enhance emmetropization in highly hyperopic (≥+5.00D) 3-month old infants. Our hypothesis is that more active and accurate accommodation, promoted with spectacle under-correction and accommodative exercises, will increase the rate of axial elongation to reduce hyperopia. The prediction is that the eye will modulate axial length by modifying ocular shape, that more accurate accommodation will be associated with creating a less oblate, more prolate eye shape that accentuates elongation. The results of this study would be clinically relevant almost immediately. Results from the proposed study would represent evidence-based guidelines for effective infant refractive care.

II. Background and Rationale. Most healthy human infants are born hyperopic, or farsighted (Mayer, Hansen, Moore, et al., 2001). The average cycloplegic refractive error for infants at birth ranges from +1.00D to +2.50D with standard deviations ranging from 1.50D to 2.50D (Cook and Glasscock, 1951; Luyckx, 1966; Mayer et al., 2001; Santonastaso, 1930; Wood, Hodi and Morgan, 1995; Zonis and Miller, 1974). Infants undergo a process called emmetropization in which their normal early hyperopic refractive error decreases over time by coordination of the development of optical power and axial length of the eye.

A majority of the emmetropization process occurs within the first 18 months of life, particularly between 3 months and 9 months of age, leaving a small window of opportunity for potential intervention (Mayer et al., 2001; Mutti, Mitchell, Jones, et al., 2005). At 18 months of age, the mean refractive error in infants is +1.10 ± 0.90D (Mutti, Mitchell, Jones, et al., 2009). Once the infant phase of the emmetropization process is complete, residual significant levels of hyperopia can persist into childhood. If hyperopia is present past the age of emmetropization, it is unlikely the child will have the ability to "grow out of" their hyperopia (Jones, Mitchell, Mutti, et al., 2005). Failure to emmetropize leaves between 7.5% and 10% of school-aged children with clinically significant hyperopia (> +2.00D) (Kleinstein, Jones, Hullett, et al., 2003; Laatikainen and Erkkila, 1980).

Hyperopic children are more at risk for developing strabismus, specifically esotropia. Studies show a dose-dependent relationship between hyperopia and the risk of developing strabismus. Children than have a refractive error between +2.00D and +3.00D are 6.4 times more likely to develop an esotropia and those with a refractive error greater than +5.00 are 122 times more likely to develop esotropia (Cotter, Varma, Tarczy-Hornoch, et al., 2011). Anker et al. found that in children who developed esotropia, 18.4% were significantly hyperopic (+4.00D) and only 0.5% were emmetropic (Anker, Atkinson, Braddick, et al., 2004). Strabismus is a risk factor for the development of amblyopia, a decrease in visual acuity that creates impaired depth perception. Just as hyperopia shows a dose-response relationship with the development of strabismus, it shows a similar relationship with the development of amblyopia (Pascual, Huang, Maguire, et al., 2014).

Uncorrected hyperopia may compromise visual comfort or visual acuity which could impede learning. Quaid and Simpson assessed school-aged children, some of which were on an Individualized Education Program (IEP) and others who were not. They found that children on IEPs had significantly greater amounts of hyperopia than children who were not on IEPs. All of the hyperopic children had poorer scores on the Convergence Insufficiency Symptom Survey, which was used off-label to determine what asthenopic complaints the children had. The hyperopic children also had a slower reading speed than non-hyperopic children (Quaid and Simpson, 2013). One group of researchers found a link between uncorrected hyperopia and academic standardized testing. Children in first through fifth grade who had

a refractive error of +1.25D or more scored significantly lower on achievement test scores (Rosner and Rosner, 1997). A recent study assessed the early literacy in 4 and 5 year old uncorrected hyperopes and emmetropes in preschool and found that children with uncorrected hyperopia of +4.00D or greater, and children with +3.00D - +6.00D who had reduced near stereoacuity or binocular near acuity scored worse on the Test of Preschool Early Literacy compared to their emmetropic peers (VIP-HIP Study Group, Kulp, Ciner, et al., 2016). The association between uncorrected hyperopia and early literacy is important and alarming. One in six children who are not reading proficiently in third grade do not graduate from high school on time, a rate 4 times greater than for those who are proficient readers (Hernandez, 2012).

There is a lot of clinical uncertainty about managing hyperopia in infants. Human studies suggest that correction of hyperopia will improve acuity and relieve the burden on accommodation. Animal studies suggest that early correction of hyperopia may impede the normal emmetropization process that reduces hyperopic refractive error during maturation (Hung, Crawford and Smith, 1995). Clinicians and researchers are often concerned that early correction of hyperopia may interfere with emmetropization's natural process in humans. Human infant studies show conflicting results. One study found that early correction did not interfere with the emmetropization process while another did (Atkinson, Anker, Bobier, et al., 2000; Ingram, Gill and Lambert, 2000).

The proposed protocol for this study differs from other early intervention studies. The current proposal will provide a greater amount of under-correction and will occur at a younger age. Results from a longitudinal study performed by the primary investigator of this study suggest that 1.00D of under-correction in a three-month old infant would result in a very small change between 3 and 9 months of age (Figure 1) (Mutti et al., 2005). Previous studies have used only 1.00 to 2.00D of under-correction in early intervention (Atkinson et al., 2000; Ingram et al., 2000). Based on the information provided in Figure 1, the range of effective emmetropization occurs between +1.00D and +4.00D of hyperopia. More aggressive under-correction (greater than 1.00D to 2.00D) would be needed in higher hyperopes to ensure that they reach the range of effective emmetropizaion between +1.00D and +4.00D. The effective range of emmetropization is addressed in more detail in Figure 2. If the emmetropization endpoint is defined as reaching a refractive error of ≤+2.00D by 18 months of age, then 80% or more of early refractive errors of +4.00D or less at 3 months of age will resolve by 18 months of age using no intervention. For early refractive error between +5.00D to +7.00D, which is what is proposed in this study, the percentage that reach the emmetropization endpoint of ≤+2.00D drops to between 50% and as low as 20%. The range of refractive errors outside of +5.00D and +7.00D appears to be outside of the effective range of emmetropization.

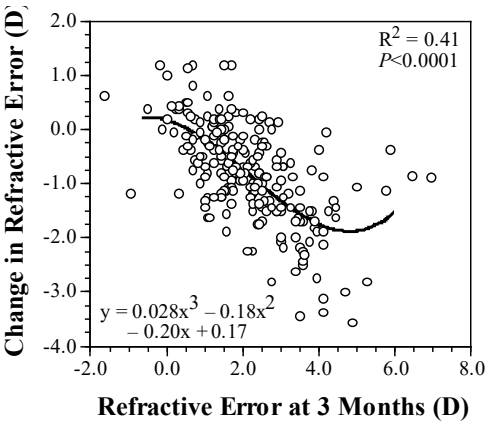

Figure 1. The change in hyperopia between 3 and 9 months as a function of hyperopia at 3 months.

Previous studies initiated early correction treatment in the latter half of of the first year of life (Atkinson et al., 2000; Ingram et al., 2000). The majority of the emmetropization process occurs before 9 months of age (Mutti et al., 2005). As children get older, hyperopia becomes less effective in promoting refractive changes. Hyperopic infants between 3 and 9 months of age show a decrease of hyperopia by an average of 0.81D while infants between 9 and 18 months show a decrease of only 0.23D (Mutti et al., 2009). Perhaps previous studies did not find a treatment effect because they initiated treatment too

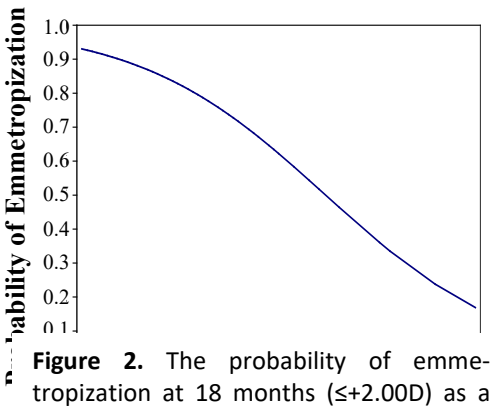

Figure 2. The probability of emmetropization at 18 months (≤+2.00D) as a function of refractive error at 3 months.

late. An animal study shows that refractive compensation occurred with moderate spectacle under-correction at the human equivalent of 2.5 months of age, which provides support for the rationale behind this early intervention study (Smith and Hung, 1999).

The foundation of this proposed project has been investigated in the past by the PI of this study, Dr. Don Mutti. The study found that partial spectacle correction and accommodation training to improve accommodative response is a promising treament in reducing high amounts of farsightedness which is illustrated in the graphs below:

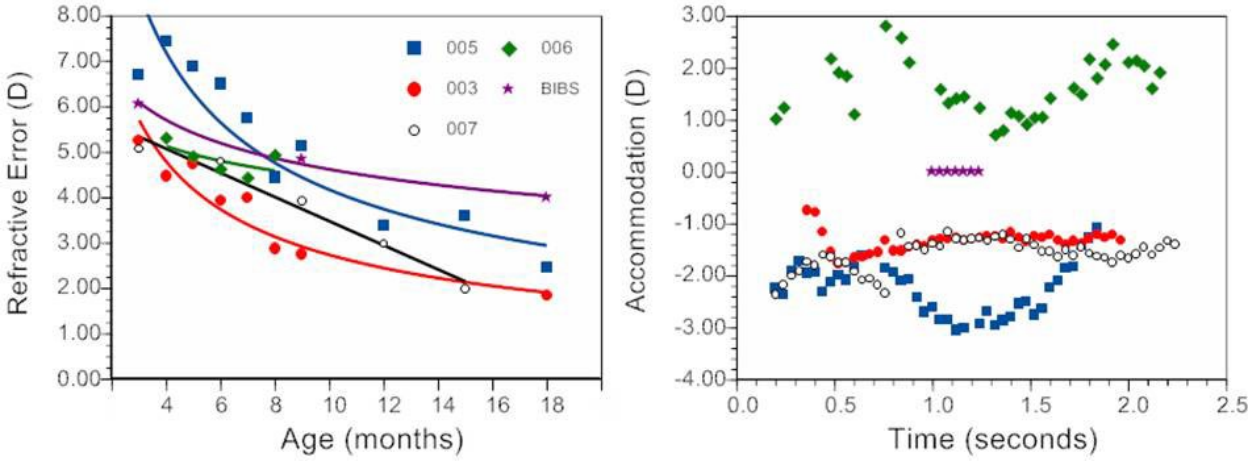

Figure 3a. Refractive error changes over time (age, in months); **Figure 3b.** Accommodation (in Diopters) dynamic state over time (in seconds).The infants treated with the proposed intervention (glasses and training; subjects 003, 005, and 007) lost more farsightedness (left panel) and had more accurate accommodative responses to a 2 diopter stimulus than untreated subjects (006 and BIBS).

In the figures, refractive error and eye focusing (accommodation) data from 4 subjects are plotted against age and time respectively. Subjects 003, 005, and 007 were given partial correction and accommodative training at 3 months of age. In Figure 3a, each of those subject's farsightedness decreased over time at a faster rate than untreated subject 006 those in the Berkeley Infant Biometry Study (BIBS) study. Figure 3b shows that subjects who appeared to have the greatest decrease in the amount of hyperopia tended to have better eye focusing ability, which is one of the proposed mechanisms of emmetropization and something we will measure longitudinally throughout the study.

III. Procedures

A. Research Design. This study will be a hybrid of a prospective, randomized, clinical trial for infants with farsightedness that is ≥ +5.00D to ≤ +7.00D and a case series for infants with farsightedness that is > +7.00D. The study will take place over 18 months.

B. Sample. Subjects for this study will be recruited from Riverside Pediatrics Associates, a local private practice in Columbus, Ohio. The physicians, nurses, and staff will help recruit eligible subjects. The infants will be screened at their 2 month old well-baby visits at the practice.

Entry Criteria are:

- Age: between 8 weeks and 15 weeks at the baseline examination
- Either gender, any ethnicity
- Birthweight greater than 2500g

- Normal pregnancy and delivery (including Cesarean section delivery but excluding serious complications or conditions such as eclampsia or rubella)
- Hyperopia of ≥ +5.00D in the spherical component of refractive error (most hyperopic meridian) in one or both eyes measured with cycloplegic retinoscopy using 1% cyclopentolate
    - Infants with a refractive error of ≥ +5.00D to ≤ +7.00D will be randomized to treatment or standard therapy (which is observation only)
    - Infants with a refractive error of > +7.00D will receive treatment
- No astigmatism greater than 2.00D in either eye
- No anisometropia greater than 1.50D (spherical equivalent)
- No strabismus or previous history of difficulty with pupillary dilation
- No history of cardiac, liver, asthma, or other respiratory disease
- No history of ocular disease, retinal detachment, severe macular dragging, intraocular surgery, optic nerve hypoplasia, malformations of the eye, cortical visual impairment or active ocular inflammation
- No history of hydrocephalus, Down syndrome, or cerebral palsy, developmental delay, or seizure disorders.

If a subject presents with conditions such as pathology, or refractive error that is significant and suggests the presence of a pathological condition, an appropriate referral will be made.

Sample size calculations were performed using the formula adapted by Lindsey to take advantage of the power gained from obtaining repeated measurements across time and eyes (Lindsey, 2001). Data from the Berkeley Infant Biometry Study (BIBS) were used to obtain an estimate of the within-subject/within-visit repeatability of refractive error and the correlation of these measurements across time. The standard deviation for change in refractive error from 3 to 9 months of age from infants with hyperopia >+5.00D enrolled in BIBS was 1.17D. Data from Atkinson et al. suggests a standard deviation of 1.50D and Ingram et al. give a standard deviation for change is assumed to be 1.36D (Atkinson et al., 2000; Ingram et al., 2000). To provide the most conservative estimate of sample size, the standard deviation of change is assumed to be 1.50D. If a new, difficult, expensive treatment strategy is to be adopted, the benefit must be substantial. The ordinary decrease in hyperopia in uncorrected, highly hyperopic infants might be 1.2D to 1.34D (Atkinson et al., 2000; Ingram et al., 2000). We would expect that there would be little enthusiasm for this new approach if the decrease in hyperopia in treated infants was not on the order of 3.00D (an improvement compared to controls of 1.75D). Using these parameters, a sample size of 13 in each randomized group will be needed (α=0.05, β=0.1, two-sided test). If we estimate that 10% of the infants may not complete the follow up, 30 infants need to be enrolled with 15 randomly assigned to each of the two randomized groups. The rather large difference relative to its standard deviation to be detected (1.75/1.50 = 1.17) along with the increase in power obtained by taking repeated refractive error measurements help to keep the sample size low. However, given the prevalence of high hyperopia (more than +5.00D) in the population of 3 months old infants, a sample size of 30 eligible infants (for randomization, not including the case series) is not trivial. Up to 10 eligible infants will be enrolled in the case series portion of the study. One of the major efforts in this project will be screening the 900 infants needed to find those that are eligible.

C. Measurement/Instrumentation

a. **Cycloplegic refractive error.** Refractive error will be measured using cycloplegic autorefraction and retinoscopy (1% tropicamide at the screening visit and 1% cyclopentolate at all follow up visits). Refractive error will also be measured with the following FDA-approved commercially available instrument:
    i. **Welch Allyn Sure Sight Autorefractor**
b. **Accommodative accuracy.** Accommodation will be assessed with the following FDA-approved commercially available instrument:
    i. **PowerRefractor**

D. Detailed study procedures

a. **Screening.** Topical tropicamide (1%) will be administered to an infant at their 2 month well-baby visit. Thirty minutes after instillation of tropicamide, the infant is placed the appropriate distance from the autorefractor and from the screener (35cm from the Welch Allyn SureSight, 67 cm for retinoscopy) for measurement of central cycloplegic refractive error. If the subject measures ≥+5.00D sphere in one or both eyes via retinoscopy, the subject's parent will be given information regarding the study. If the parent(s) decides to participate, Dr. Ann Morrison (co-investigator) will schedule the patient and infant for the treatment phase of the study.
b. **Treatment**
    i. **Randomization.** Subjects will be randomized to treatment or placebo (control) if their refractive error is ≥ +5.00D to ≤ +7.00D via retinoscopy. A random number generator will be run in SAS using the RANUNI function prior to the start of the study. Random numbers will be generated for 30 subjects (15 for each arm of the study), in a manner in which half of the numbers are even and half of the numbers are odd. In the program, it will be specified that there should be 15 subjects in each arm of the study giving a total of 30 subjects. The program will then scramble numbers in random to provide 15 subjects in each arm. In order from the sequence of random numbers, even numbers will represent subjects assigned to treatment and odd numbers will represent subjects assigned to the control group (standard therapy – observation).

    Subjects with a refractive error of +7.00D or higher will receive treatment as a Case Series.

    ii. **Treatment group**. Infants randomized to the treatment will receive spectacles with 3.00D of under-correction relative to the spherical equivalent in each eye as measured by cycloplegic retinoscopy performed at baseline. The level of correction of astigmatism is more complicated. Clinicians report a wide range of philosophies with respect to the correction of astigmatism in the young patient (Lyons, Jones, Walline, et al., 2004; Miller and Harvey, 1998). These philosophies tend to differ between the professions of optometry and ophthalmology; the majority of optometrists prescribe less than the full amount of astigmatism while the majority of ophthalmologists prescribe the full amount of astigmatism. Neither the *American Academy of Ophthalmology* nor the *American Optometric Association* make explicit recommendations in their practice guidelines as to whether to provide the full cylindrical correction or to reduce this correction by some formula. Anker et al. only provided half the measured cylindrical error in the spectacles while Ingram et al. fully corrected the astigmatism (Anker et al., 2004; Ingram et al., 2000). Considering the lack of consensus

and that advantages may accrue from having the most in-focus retinal image, the treatment group in the current study will receive the full amount of measured astigmatism in their glasses.

Children with anisometropia > 1.50D will be excluded from the study as this amount is a risk factor for accommodative esotropia (Weakley, Birch and Kip, 2001). Present in only 1% of infants, this amount of anisometropia is rare (Mayer et al., 2001). Changes in spectacle lens power will be made as needed at any follow-up visit to keep the level of under-correction within 0.50D of the target 3.00D. Follow-up will occur with a phone call to the subject's parent(s) after the first week of spectacle wear to assess the adaptation to the spectacles and to address their acceptability. If the subject's parent(s) feel that there is an issue with spectacle wear adaptation, they can return to the clinic to assess the prescription and fit of the spectacles. If the parent(s) feel that spectacle wear is going well, follow-up will then continue at 4.5 months of age, 6 months of age, 9 months of age, 12 months of age, 15 months of age and 18 months of age. If an infant in the treatment group develops a spherical equivalent refractive error less than +3.00D in both eyes, he or she will be considered to have emmetropized, be taken out of spectacles, and then followed until the conclusion of the study (when the subject is 18 months of age). If only one eye achieves the emmetropization endpoint, the non-emmetropizing eye will remain under treatment with correction equal to the difference in refractive error between the two eyes, up to and including 1.00D. For example, an infant who is +3.50D OD and +2.75D OS would receive a +0.75D for the right eye and a plano lens for the left eye. While this places the level of under-correction below 3D, the importance of maintaining a balanced correction requires such an adjustment. Aggressive under-correction is intended to be only temporary, ending when the potential for emmetropization is complete. Regular clinical care will replace any investigational treatment at the conclusion of the 15 month follow up at 18 months of age.

Parents of the subjects in the intervention group will be instructed to provide 20 minutes per day of visual engagement with their infant to encourage accurate accommodation. The visual engagement exercises are listed specifically on the "Visual Engagement Activities" form that will be given to parents at the initiation of treatment. Parents are instructed that the subject should wear his or her correction when possible while performing visual engagement activities.

Compliance of glasses wear will be encouraged with parents. A calendar will be given to the parents at each visit to help keep track of the subject's compliance with glasses wear and prescribed vision therapy. Compliance will be monitored but infants will not be discontinued from the study for non-compliance with glasses wear.

iii. **Control group – Standard Therapy.** Infants typically do not receive comprehensive eye examinations. Therefore infant hyperopia is most often neither detected nor corrected in the US at this time. Uncorrected infant hyperopia has no symptoms. Infant eye examinations are typically done only when a child presents with strabismus or pathology. As an example,

none of highly hyperopic (>+4.00D) three-month-olds from the BIBS study referred for clinical assessment received at correction from community eyecare providers. Therefore the current standard for treating hyperopia against which any new treatment must be judged is observation without correction. The alternative would be to provide full or 1.00D under-correction. It has already been shown that infants may not emmetropize with these corrections (Atkinson et al., 2000). Any inhibition of emmetropization may be accentuated if infants are corrected in this way at three months rather than later. Infants with no correction may occasionally emmetropize (Ingram et al., 2000). This suggests that the most ethical and informative form of standard therapy for infant hyperopia would be to provide no correction for the infants within the range of eligibility (≥+5.00D to ≤+7.00D). Beyond the upper limit of eligibility for randomization (≥+7.00D), the majority of both optometrists and ophthalmologists would recommend providing a refractive correction, making randomization of infants to observation only questionable ethically (Lyons et al., 2004; Miller et al., 1998). Therefore, these infants will be given treatment (like the treatment group) and observed as a Case Series to better understand the nature of their refractive error development.

Infants with refractive errors from +5.00D up to +7.00D who are randomized to standard therapy will receive no correction. Follow-up will occur on the same schedule as infants randomized to treatment: 1.5 months after the baseline examination and then every 3 months until completion at 18 months of age (6 follow-up visits after the baseline exam). Regular clinical care, if any is needed, will begin at the conclusion of follow up at 18 months. Infants in either the treatment or control group who have not achieved a refractive error of <+3.50D in each eye by 18 months of age will be referred outside the study for an independent evaluation. This level of hyperopia is selected for referral at 18 months because of its association with an elevated level of risk for strabismus (Atkinson, Braddick, Robier, et al., 1996)

iv. **Case Series Group.** Infants with a refractive error of ≥+7.00D will receive treatment (same protocol as infants randomized to the treatment group of this study). The follow-up of the infants in this case series group is the same for those who are randomized to treatment.

c. Measurements. The subject will be examined while seated in the parent's lap for all tests.

i. Visual Acuity. Preferential looking visual acuity with **Teller acuity cards** will be used to determine visual acuity without refractive correction. The Teller acuity cards will be presented at 55cm. The subject is observed through a center peephole of the acuity cards for preferential looking. Successively smaller patterns are presented until the subject either no longer displays preferential looking, or loses interest. Testing will be first be attempted monocularly but if the subject is resistant to occlusion, testing will be done binocularly. Final results are recorded in the subject's chart as the cycles/degree of the last card at which a response is noted in each eye.

ii. Pupil testing. Pupillary function is tested with a penlight for size, equality, shape, response to direct light, and consensual response.

iii. **Version testing.** Versions are tested, with the examiner looking for any restrictions of yoked eye movements as the baby looks in different fields of gaze.

iv. **Binocularity testing.** The examiner will determine if strabismus is present using a unilateral cover tests as well as Hirschberg evaluation. Subjects with an existing strabismus are not eligible. Subjects who develop a strabismus during the study period will be refereed for further evaluation and retained for follow up.

v. **Accommodative response and lag** will be measured with the Schaeffel PowerRefactor and by dynamic retinoscopy with no refractive correction worn.

The Schaeffel PowerRefractor is an infrared, binocular photoretinoscope capable of measuring the meridional refractive error, and therefore the dynamic accommodative response, of both eyes simultaneously at 25 Hz. Photorefraction in general and this instrument specifically have been shown to compare well to conventional retinoscopic measures of accommodation with the added advantage of measuring accommodative response and its variability in both eyes over a more extended period of time (Blade and Candy, 2006; Braddick, Atkinson, French, et al., 1979; Howland, Dobson and Sayles, 1987; Rosenfield, Portello, Blustein, et al., 1996; Seidemann and Schaeffel, 2003). The PI's experience with this instrument is that maintaining attention is critical to the validity of measurements. Inattention and the drifting of gaze from central fixation on the accommodative target interfered with the comparability of measurements to conventional dynamic retinoscopy (Gabriel and Mutti, 2009). To filter out readings that might be obtained when fixation is poor, the "Gaze Control" setting on the PowerRefractor will be set to 15° in "Binocular" refraction mode.

The accommodative targets are a set of plush stuffed toys. The texture of the toy maintains a range of spatial frequencies available to the baby that scale with fixation distance to drive the accommodative response. Such targets have been used successfully by the PI and another laboratory in studies of infant accommodation (Blade et al., 2006). A large circular "hot" infrared reflecting mirror is positioned at 45° in front of the infant. The reflecting mirror allows the accommodative target to be positioned in real space in front of the infant along the line of sight and coincident with the axis of the photorefractor. This avoids problems with fixation drifting from the 15° limit set on the machine. The PowerRefractor is placed on an instrument table 1 meter away from the subject on the other side of the mirror. The proximity of the mirror to the infant means that only a maximum of 4D of accommodation can be stimulated. Readings will be taken for approximately one minute at each of two distances: **6 meters and 0.33 meters**. Filtering of the data will remove blink artifacts or non-physiologically rapid changes in accommodative response (>10D/sec) (Harb, Thorn and Troilo, 2006).

Dynamic Retinoscopy will be assessed like a modified monocular estimation method (MEM), which is commonly used in clinical practice. Dynamic retinoscopy has been found to be similar to objective accommodative measurements, which we are measuring with the

PowerRefractor (Gabriel et al., 2009). Dynamic retinoscopy would be more directly applicable to clinicians who see patients regularly and do not have access to an instrument that can measure accommodation objectively in a clinical setting. Measurements will be obtained at **0.33 meters.**

There is no universally accepted outcome measure for infant accommodative response, therefore the analysis in this phase will be somewhat exploratory. The simplest metric to calculate would be the average accommodative response. However, variability in that response provides a useful perspective that distinguishes the infant with stable accommodation from the one that is less well-controlled or exhibits more of a searching accommodative behavior. Variability will be added as a covariate in analyses of the accommodative response. The simple standard deviation in accommodation is one measure of this variability. Another approach would be to look for periodic variability through Fourier analysis of the response. This analysis would be exploratory. Analyses are typically of 10 second segments of response. If infants are too unsteady to give such lengths of uninterrupted data, then the analysis may not be feasible. If the analysis can be done, then power at low, mid, and high temporal frequencies will be used as covariates in the analyses of accommodative response. Other potential metrics might be lag-minutes or diopter-minutes, essentially area-under-the-curve summary measures of diopters of lag, or alternatively, diopters of accommodative response per minute of recording.

vi. **Cycloplegic refractive error** will be measured at all visits. Refractive error will be measured by **cycloplegic retinoscopy** by a masked examiner (primary outcome of the treatment phase of the study). The parents of the subject will be instructed not to discuss the treatment group the patient is in to the masked examiner. Measurements will occur 30 minutes after drop instillation. One drop of proparacaine 0.5% will be instilled in each eye, followed by two drops of cyclopegic agents. The drops used for cycloplegia are the following:
    1. Tropicamide (1%) will be used only at the screening visit
    2. Cyclopentolate (1%) will be used during all remaining visits

    The neutral point for the horizontal meridian is recorded first, then the neutral point for the vertical meridian. If the axes are oblique, the true meridian is measured by projecting the retinoscopy beam on to a protractor on the wall. **SureSight autorefraction** will be also be performed on both eyes from 35cm by the investigator (unmasked).

vii. **Peripheral refractive error.** Peripheral refractive error will be assessed by the examiner using the SureSight autorefractor as an estimate of the ocular shape during emmetropization. The subject's gaze is directed towards toys or interesting targets. Measurements will be made at 30° in both left and right gaze (a total of 2 peripheral gazes). This will be measured at the baseline, 9 month, and 18 month visit.

viii. **Parental refractive error status**. The parent(s) refractive error will be obtained as in the Berkeley Infant Biometry Study (BIBS), from the prescription for glasses provided by the eye care provider for parents who wear refractive correction. If the parents report not having had a recent eye

examination, refractive error status will be estimated with the autorefractor without cycloplegia.

ix. **Survey.** Additional data will be collected via a survey administered at the baseline visit and will request information regarding:
   1. Parental age at the infant's birth
   2. Parental smoking status
   3. Alcohol consumption
   4. Infant birthweight
   5. Birth order
   6. Minor complications of pregnancy and delivery
   7. Years of education completed for each parent
   8. Family income
   9. Ethnic identification for each parent and for the child (assigned by the parent)

x. **Additional data.** The following data will be obtained at each visit:
   1. Significant infant illness
   2. Medications given to the infant
   3. Nutritional history
   4. Compliance with spectacle wear. Parents will fill out a form at each follow up visit listing how compliant the subject was wearing spectacles. Parents of the subjects will be able to classify compliance as very good (≥75% of the time), good (≥50% of the time but less than 75% of the time), fair (≥25% of the time but less than 50% of the time), or poor (≤25% of the time). Parents will be given a pre-printed calendar to help them keep track of compliance on a daily basis. This will be turned into the investigator at the next follow up.
   5. Compliance with visual engagement and vision therapy exercises. Parents will out a form at each follow up visit listing how compliant they were with performing accommodative therapy with the subject. Parents of the subjects will list how many minutes they were able to engage in the recommended visual activity each day. Parents will be given a pre-printed calendar to help them keep track of compliance on a daily basis. This will be turned in to the investigator at the next follow up.

xi. **Ocular health**. The ocular health will be assessed at the baseline examination and at the final visit with a direct ophthalmoscope, transilluminator with a 20 Diopter condensing lens, or binocular indirect ophthalmoscope.

d. Measurement and Visit Schedule

Measurement	S	V1/B	V2	V3	V4	V5	V6	V7
Target Age (months)	2	3	4.5	6	9	12	15	18
Cycloplegic refractive error w/ SureSight	X		X	X	X	X	X	X
Cycloplegic refractive error w/ Retinoscopy	X	X	**M**	**M**	**M**	**M**	**M**	**M**
Peripheral Refractive error w/ Sure Sight		X			X			X
Accommodative response and lag w/ Power Refractor		X	X	X	X	X	X	X

Accommodative response and lag w/ MEM		X	X	X	X	X	X	X
Ocular Health		X						X
Ocular Motility		X	X	X	X	X	X	X
Ocular Alignment		X	X	X	X	X	X	X

LEGEND: **S** = Screening visit at Pediatrician's office
V1/B = Baseline Examination
V2 = Visit 2, 4.5 months of age **V3** = Visit 3, 6 months of age
V4 = Visit 4, 9 months of age **V5** = Visit 5, 12 months of age
V6 = Visit 6, 15 months of age **V7** = Visit 7, 18 months of age
M = Performed by an examiner masked to the infant's group assignment

e. Visit Schedule. The target and acceptable dates for each study visit are given below. If a monthly examination cannot be completed within the acceptable range, that visit will be considered as missed. It will be important to stress to parents at enrollment the importance of attending each of these scheduled visits. The acceptable range for the 6 and 18 month examinations has been extended to 14 days after the target date to maximize the probability that this examination can be completed.

An attempt will be made to dispense spectacles at the baseline examination. A stock of frames and lenses will be kept on site. If available, the investigator will edge lenses the day of the baseline examination (Visit 1) and dispense the glasses the same day. If the frame and/or lenses are not in stock, they will be ordered the day of the baseline examination (Visit 1) and the subject will return for a dispensing visit. The investigator will call the parents of the subject a week after glasses wear to make sure the glasses fit acceptably and the subject is not having difficulty adapting to glasses wear. A spectacle recheck visit will only occur if there are problems with adaptation to glasses wear. The investigator will decide at that visit if a cycloplegic refraction needs to occur with 1% cyclopentolate and if the lenses or frame need to be replaced.

Study Visit	Target Date	Visit Window
Visit 1/Baseline examination (V1)	Age 3 months	±21 days
Dispensing visit	Within 3 days **(B)**	±7 days **(B)**
Spectacle recheck visit*	7 days **(D)**	4 to 10 days **(D)**
Month 1.5 examination (V2)	45 days **(B)**	38 to 52 days **(B)**
Month 3 examination (V3)	90 days **(B)**	83 to 97 days **(B)**
Month 6 examination (V4)	180 days **(B)**	173 to 194 days **(B)**
Month 9 examination (V5)	270 days **(B)**	263 to 277 days **(B)**
Month 12 examination (V6)	360 days **(B)**	353 to 367 days **(B)**
Month 15 examination (V7)	450 days **(B)**	443 to 464 days **(B)**

LEGEND: **B** = from date of Baseline Examination
D = from date of Dispensing visit
***** = not required

f. **Development of Strabismus.** The subject population of this study is at risk for developing strabismus (Anker et al., 2004; Cotter, 2007; Pascual et al., 2014). This will be discussed with the parents of potential subjects during screenings and during the consent process prior to the baseline examination. If a subject develops a strabismus, the subject will be discontinued from treatment in the study. The subject cannot remain in either arm of the study because of the different standard of care in prescribing philosophy that occurs with the development of strabismus (typically providing a full refractive correction for hyperopia). The subject will remain in the study and will continue to be followed for observation of all study measurements and outcomes. The subject's parents will have the option of their child remaining under the care of Dr. Ann Morrison in the Ohio State University College of Optometry Pediatric clinic, or any other doctor within the Ohio State University College of Optometry, or seek or be referred to another provider for a second opinion or for patient care. Any visits or treatment of strabismus or any clinical sequelae of the strabismus would be at the discretion of the licensed eye care provider and separate from the study. Follow up visits related to the study will follow the same schedule and contain the same measurements listed in the protocol.

E. Internal Validity. There are no threats to internal validity. All procedures performed in the examination are standard procedures that have been performed frequently in other studies. Threats to external validity might be present in selection bias. The sample of patients to be recruited will be identified at Riverside Pediatrics Associates by screenings of age appropriate infants. The screenings will be performed by Dr. Ann Morrison, Dr. Mike DiBartola, or a nurse that has been adequately trained. The age, gender, and ethnicity of these patients might not be a true representation of the general population of full term, healthy infants.

F. Data Analysis. All data analysis will be performed using SPSS (Version 24). Statistical significance will be assessed using two-sided tests with an alpha level of 0.05. Data from both eyes will be included in all analyses and techniques to control for intra-subject correlations will be used.

The basic analysis will be a two-sample t-test comparison of the change in refractive error between the two groups at 9 months and again at 18 months of age. Analysis of Covariance (ANCOVA) will be used to compare the change in refractive error between the two treatment groups adjusting for any possible confounding variables. Refractive error at 3 months along with any other identified confounders will be included as covariates in the analysis. Randomization of infants into the two treatment groups should protect against confounding, however, testing will be performed and adjustments made for imbalances in confounders between groups.

The relationship of accommodative effort and accommodative lag with change in refractive error between 3 and 9, or 3 and 18 months will be analyzed by repeated measures analysis of variance. We will fit a linear functions describing the relationship between change in refractive error and accommodation as the repeated factor, either effort or lag. A significant effect for type of accommodation will indicate that the greater slope is the better explanation of the driving force for change in refractive error.

Relative peripheral refractive error will be calculated as the difference in peripheral and central cycloplegic refractive error. This relative peripheral refractive error calculation will give insight into the ocular shape of the subject. If the relative peripheral refractive error is relatively myopic compared to the central refractive error, the eye has a more oblate shape. If the relative peripheral refractive error is relatively hyperopic compared to the central refractive error, the eye has a less oblate or more prolate shape. The relationship of the change in peripheral refractive error and central refractive error (relative peripheral refractive error) will be analyzed by a two-sample t-test comparison of the change in the relative peripheral refractive error between the two groups at 9 months and again at 18 months of age. Analysis of Covariance will be used to compare the change in relative peripheral refractive error between the two treatment groups adjusting for any other possible confounding factors. Peripheral refractive error at 3 months along with any other identified confounders will be included as covariates in the analysis. Randomization of infants into the two treatment groups should protect against confounding, however, testing will be performed and adjustments made for imbalances in confounders between groups.

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