Bifocal & Atropine in Myopia (BAM) Study
NCT03312257
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Manual of Procedures

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Contents

Chapter 1: Study Synopsis

Purpose of the Investigation

Myopia affects approximately one-third of the United States population (Vitale et al. 2008), which is an increase from 25% of the population reported in the 1970s and 1980s (Sperduto et al. 1983; Vitale et al. 2009). Although blurred distance vision caused by myopia is relatively easy to correct with spectacles, contact lenses, or refractive surgery, myopia costs the United States approximately $4.6 billion annually (Javitt and Chiang 1994), high myopia is associated with increased risk of glaucoma (Loyo-Berrios and Blustein 2007; Lee et al. 2008), retinal detachment (Hyams and Neumann 1969; Eye Disease Case-Control Study Group 1993), chorioretinal atrophy (Curtin 1985), and decreased quality of life (Rose et al. 2000; Erickson et al. 2004; Chen et al. 2007). Thus, slowing the progression of myopia could potentially affect a large proportion of the population and reduce the negative side effects that accompany the disease.

Both atropine and soft bifocal contact lenses have been shown to slow myopia progression, and both can cause changes in the thickness of choroid (Read et al. 2010; Chakraborty et al. 2012; Chakraborty et al. 2013; Nickla et al. 2013), which has been suggested to serve as a signal mediator to regulate eye growth. But the relationship between these mechanisms is unclear. The central hypothesis to be tested is that atropine and soft bifocal contact lenses each exert their anti-progression actions through a common pathway that involves the choroid. If this is correct, then adding atropine treatment to soft bifocal contact lens wear will lead to a more effective slowing of myopia progression than prescribing soft bifocal contact lenses alone due to the additive effects in the common pathway. Determining whether these hypotheses are true will have significant implications for future studies to develop and test new therapeutic regimes that optimize the effect of myopia control through combined pharmacological and optical interventions.

Chapter 2: Specific Aims

I propose a clinical study in patients with myopia to investigate the effect of a novel clinical intervention on myopia progression. Atropine, a non-selective muscarinic receptor antagonist, provides the most effective myopia control in humans when prescribed in 0.5% or 1% concentration. However, the side effects – loss of accommodation and pupil dilation – make it impractical for clinical use. Recently, low concentration atropine (0.01%) was shown to slow myopia progression by about 60% while significantly mitigating side effects in children. The precise site of action involved in slowing myopia progression with atropine remains controversial. Some authors state that atropine may slow myopia progression through antagonist effects on retinal muscarinic receptors, but others suggest that atropine may slow myopia via non-muscarinic and non-retinal mechanisms. Center distance design soft bifocal contact lenses have also been shown to slow myopia progression in children by an estimated 40% with few side effects. The mechanism for this treatment effect is most likely the myopic defocus (light focused in front of the retina), a robust growth-inhibiting signal, presented to the retina by the add (near) power of the contact lens.

Both atropine and optical defocus can cause changes in the thickness of choroid, which has been suggested to serve as a signal mediator between retina and sclera to regulate eye growth. Intravitreal injection of atropine in chicks results in rapid, transient choroidal thickening and slowed axial elongation. Additionally, the choroid thickens and thins in response to short-term optically induced myopic and hyperopic defocus, respectively. We therefore postulate that in response to the signal cascades triggered by atropine and soft bifocal contact lens wear, the choroid adjusts its thickness and transfers growth-modulating signals to sclera.

My central hypothesis is that pharmacological and optical treatments exert their anti-myopia actions through a common pathway that involves the choroid. I propose that adding atropine treatment to soft bifocal contact lens wear will lead to a more effective slowing of myopia progression than prescribing soft bifocal contact lenses alone due to the additive effects in the common pathway. Alternatively, if we find that combined treatment is no more effective than soft bifocal contact lenses alone, that would suggest a saturated effect of this shared mechanism.

To test these hypotheses, I will enroll 52 myopic children aged 7 to 11 years into a treatment protocol of wearing soft bifocal contact lenses in combination with daily administration of one drop of 0.01% atropine for three years. The rates of myopia progression and axial elongation will be compared to the rates in age-matched subjects who are receiving treatment with only soft bifocal contact lenses in the Bifocal Lenses In Nearsighted Kids (BLINK) Study (U10EY023208). The BLINK Study is a multi-center, randomized clinical trial chaired by my primary mentor, and it was designed to test the hypothesis that the peripheral myopic defocus produced by the add power of soft bifocal contact lenses is responsible for slowing myopic eye growth.

Aim 1. To test whether the combined treatment of 0.01% atropine and soft bifocal contact lens wear produces slower myopia progression and axial elongation compared to soft bifocal contact lenses alone over 3 years. I will compare the three-year change in spherical equivalent refractive error and axial length of subjects undergoing the combined treatment to age-matched subjects wearing only soft bifocal contact lenses in the BLINK Study.

Aim 2. **To test whether early changes in choroidal thickness can be used as predictors of long-term myopia progression / axial elongation.** I will measure the change in choroidal thickness from baseline to 3 weeks in the subjects receiving combination treatment and in the BLINK Study subjects using soft bifocal contact lenses alone. I will then determine whether the amount of 3-week change in choroidal thickness correlates with the 3-year rate of myopia progression / axial elongation in each group.

Scientific & Clinical Impact: The results of this study will have significant implications for future studies to develop and test new therapeutic regimes that optimize the effect of myopia control through combined pharmacological and optical interventions. The outcomes will also aid in understanding the potential role of short-term changes of choroidal thickness in long-term regulation of myopia progression and ocular growth.

Chapter 3: Study Design

This proposed experiment is an ancillary study of a multi-center, randomized clinical trial Bifocal Lenses In Nearsighted Kids (BLINK) Study (U10EY023208), which compares myopia progression rate between subjects wearing single vision contact lenses and those wearing soft bifocal contact lenses. The BLINK Study will enroll 294 myopic children aged 7 to 11 years at two clinical centers: The Ohio State University (OSU) College of Optometry and The University of Houston College of Optometry (UHCO).

The subjects in the BLINK Study will be randomly assigned to wear either single vision soft contact lenses or soft bifocal contact lenses with either a +1.50 D add or +2.50 D add power for at least three years, with 49 subjects in each treatment arm at each clinical center. This proposed study will recruit one group of 52 additional subjects that meet BLINK eligibility criteria and that are age-matched with a comparison group -- 49 BLINK study participants who are wearing soft bifocal contact lenses with +2.50 D add power.

The subjects in this proposed study will wear soft bifocal contact lenses in combination with daily administration of 0.01% atropine for three years. The rates of myopia progression and axial elongation will be compared to those in the comparison group in the BLINK Study. The protocol for the outcome measures in this proposed project is consistent with the BLINK Study.

Chapter 4: Statistical Analysis Plan

The sample size calculations for all Specific Aims were performed using PASS 2005 (Hintze J, 2007) software using α = 0.05 and β = 0.20 (power =80%) and then combined to determine the optimal sample size to address all of the aims. Estimates of sample size were computed for each specific aim, as follows:

Specific Aim 1: To test whether the combined treatment of 0.01% atropine and soft bifocal contact lens wear produces slower myopia progression and axial elongation compared to soft bifocal contact lenses alone over 3 years.

For Aim 1, the sample size is driven by the desired difference in spherical equivalent progression between the two groups. This difference needs to be of a magnitude that is considered clinically relevant. Walline and colleagues showed that the mean (± SD) myopia progression of single vision soft contact lens wearers was -1.29 D ± 0.71 over three years (Walline et al. 2008). The proposed myopia progression in the +2.50 D add soft bifocal group for the sample size calculation of the BLINK Study based on a treatment effect of 50% was -0.65 D. A reasonable reduction in myopia progression from the addition of atropine to the +2.50 D add bifocal lenses would be about 0.33 D, an additional reduction of 50%. Using a standard deviation of 0.71 D and taking into account the pair-matched design, the sample size for this aim would be 39 subjects per group.

Specific Aim 2: To test whether early changes in choroidal thickness can be used as predictors of long-term myopia progression / axial elongation.

For Aim 2, the correlation between choroidal thickness and refractive error / axial length ranges from 0.35 to 0.74 based on previous studies (Nishida et al. 2012; Flores-Moreno et al. 2013; Vincent et al. 2013). A sample size of 44 per group will allow for detecting a correlation of 0.41 between short-term changes in choroidal thickness and long-term myopia progression / axial elongation.

Sample Size Conclusion

Using the maximum required sample size (39 subjects for aim 1, and 44 for aim 2) and adjusting for 18% loss to follow-up gives a total sample required of **52**.

Chapter 5: Eligibility

In order to participate in the study, all subjects must meet the following criteria at Visit 1:

Age at baseline examination	7 to 11 years of age, inclusive
Spherical component of refraction	–0.75 to –5.00 D in each eye, inclusive, cycloplegic autorefraction
Astigmatism	≤1.00 DC in each eye, cycloplegic autorefraction
Anisometropia	≤2.00 D, based on spherical component
Best-corrected visual acuity (VA)	+0.1 logMAR or better in each eye at distance
VA with bifocal contact lens	+0.1 logMAR or better OU with +2.50 D add bifocal contact lenses at distance and near
Contact lens fit	The +2.50 D add soft bifocal contact lens must provide adequate movement and centration for continual wear
Compliance with atropine	Finish at least 85% of 0.01% atropine during the run-in period (see description in text)
History of vision correction	By patient report, not more than one month of gas permeable, soft bifocal, or corneal reshaping contact lens wear.
Myopia control	By patient report, not more than one month of participation in myopia control with treatments including, but not limited to, soft bifocal or orthokeratology contact lenses, atropine, bifocal spectacles
Ocular health	No eye diseases or binocular vision problems that may affect vision or contact lens wear (e.g. strabismus, amblyopia, etc.)
Ocular surgery	No previous intraocular or corneal surgery
Systemic health	No systemic diseases that may affect vision, vision development, or contact lens wear (e.g. diabetes, Down's syndrome, etc.)
Medications	No chronic use of medications that may affect immunity, such as topical or systemic use of corticosteroids
Participation	Agree to participate in the study for three years

For participants who meet the above eligibility criteria except "compliance with atropine" at the baseline visit, we will schedule a 1-week follow-up visit for atropine dispensing as well as contact lens insertion, removal, and care training. At the 1-week Visit, we will prescribe a 2-week supply of 0.01% atropine and give instructions on how to use the eye drops and the side effects of atropine. The participants will be asked to use atropine for 2 weeks (**run-in period**) and then return to clinic to determine final eligibility. We will weigh the atropine with its bottle before giving it to the participant, and ask the participants to bring the remaining atropine to the clinic at the 3-week Visit. We will weigh the remaining atropine with its bottle, and subjects who finish at least 71% of the atropine eye drops based on the weight during the run-in period (missing drops no more than 2 days per week on average) will be eventually enrolled in the study.

Chapter 6: Outcome Measures

There are nine scheduled visits during the BAM Study. Outcome measures are completed at every visit, but the primary outcome measures will be conducted at the baseline and annual visits. Visits are listed by number in Table 6-1.

Table 6-1: Visit numbers and timing of the visit.

Visit Number	Timing
1	Baseline
2	1 week
3	3 weeks
4, 6, 8	6, 18, and 30 month visits
5, 7, 9	1, 2, and 3 year visits

Procedures performed at each visit are noted in Table 6-2.

Table 6-2: Schedule of measurements for the study. Cycloplegic autorefraction is the primary outcome.

	Visit 1	Visit 2	Visit 3	Visits 4, 6, 8	Visits 5, 7, 9
Manifest refraction (OU)	X				
Spherical over-refraction (OU)			X	X	X
High contrast VA (OU) OD/OS at baseline	X (M)		X (CL)	X (CL)	X (CL)
Low contrast visual acuity (OU)	X (M)		X (CL)	X (CL)	X (CL)
Near visual acuity (OU)	X (M)		X (CL)	X (CL)	X (CL)
Modified Thorington	X (M)		X (CL)		X (CL)
Acc lag and peripheral defocus with CL, near (OD)			X		X
Contact lens centration, movement (OU)	X	X	X	X	X
Choroidal thickness (OD)		X	X		X
Slit lamp examination (OU, no contact lens)	X	X	X	X	X
Pupil size (OD)	X		X	X	X
Non-cycloplegic autorefraction (OU)	X			X	X
Manifest refraction (OU)					X
Accommodative Lag with Manifest (OD)	X				
Cycloplegic autorefraction (1° outcome, OU)*	X				X
Peripheral refractive error without CL (OD)*	X				X
Axial length (OU)*	X				X
Peripheral eye length (OD)*	X				X
Videophakometry*	X				X
Peripheral defocus with CL (OD)*	X				X
Intraocular pressure (OU)*	X		X	X	X
Dilated fundus examination (OU)*	X				X
Contact Information Form	X				X
History Form	X				
Myopia Risk Factor Form	X				X
CISS Form	X		X	Visit 4 only	X
Contact Lens Form			X	X	X
Atropine Side Effect Survey	X		X	X	X
Compliance Forms (Contact Lens & Atropine)			X	X	X
Insertion, Removal, and Care Training		X			
Approximate Length of visit (hours)	2.5 to 3.0	1.0 to 1.5	1.0 to 1.5	1.0	2.5 to 3.0

CL = contact lens; M= Manifest refraction; * = cycloplegic; Acc = accommodative

At Visit 1, we will measure high contrast distance visual acuity with the manifest refraction to determine eligibility. We will also measure low contrast and near visual acuities with the manifest refraction to determine the subjects' best

attainable visual acuity. We will also measure each of the visual acuity measures with habitual contact lenses and spherical over-refraction in place at Visits 3 through 9 in order to compare visual acuity, while controlling for myopia progression.

We will measure the axial length, videophakometry, peripheral refractive error without contact lens, peripheral eye length, peripheral defocus with contact lens at distance, peripheral defocus with contact lens at near, pupil size, and near phoria at Visits 1, 5, 7, and 9 to determine the peripheral optical profile and the growth of the eye. We will measure accommodative lag at Visit 3 to give subjects time to adapt to their contact lenses, and at Visits 5, 7, and 9. We will perform a slit lamp biomicroscopy examination at every visit.

Compliance surveys will be completed at Visits 3 through 9 in order to determine whether compliance with contact lens and atropine is associated with myopia control effects. The potential side effects of atropine eye drops will be monitored by completing a symptom survey at Visits 2 through 9.

During Visit 1, the informed consent process requires approximately 20 minutes. The non-cycloplegic portion of the examination at Visits 1, 5, 7, and 9 requires 35 minutes. Achieving cycloplegia requires 30 minutes, and the cycloplegic portion of the examination at Visits 1, 5, 7, and 9 requires approximately 65 minutes. The CISS survey and the dilated fundus examination may be completed while waiting for cycloplegia to gain maximal effect. The total time for Visit 1 will therefore be approximately 2 ½ to 3 hours. We help maintain subjects' interest by providing snacks and/or conducting contact lens care instruction during a follow-up visit if the subject becomes too tired to continue.

To reduce time for subjects, all secondary outcomes, except axial length, will be measured on the right eye only. We will dispense contact lenses and conduct contact lens care training at Visit 2 in order to shorten Visit 1 and to allow the subject to learn contact lens insertion, removal, and care while their eyes are not dilated.

Chapter 7: Visit Schedule

The initial screening will take place during a phone call to increase the likelihood that subjects who are examined at the clinic are eligible to participate in the study. The following responses must be received in order to be eligible to attend the baseline visit (Table 7-1). If the subject passes the phone screen, a Visit 1 appointment should be scheduled.

Table 7-1: Questions with answers required in order to schedule the subject for a Baseline Examination.

Age 7 to 11 years, inclusive, on the day of the baseline examination	Yes
Myopia (based on prescription from eye doctor or read by parent)	–0.25 to –6.00 D
Astigmatism (based on prescription from eye doctor or read by parent)	Less than –1.50 DC
Has your child worn gas permeable, soft bifocal, or orthokeratology contact lenses for >1 month?	No to all
Has your child used any type of myopia control (bifocal spectacles, atropine, etc.) for >1 month?	No
Does your child have an eye turn, lazy eye, or other condition that might affect study involvement?	No
Does your child have any health problems like diabetes that might affect study involvement?	No
Does your child require consistent use of oral or eye steroid medications for any condition?	No
Do you agree to have atropine eye drops put in your child's eyes every night before bed for 3 years?	Yes
Do you anticipate anything that would prevent you from participating in the study for 3 years?	No

The procedures and tests performed at Visit 1 include informed consent procedures, all measurements needed to determine eligibility, refraction, dilated fundus examination, and measurement of outcome variables. For participants who meet the eligibility criteria listed in Chapter 5 except for "compliance with atropine" at the baseline visit, we will schedule a 1-week follow-up visit for atropine dispensing to determine final eligibility (see details in Chapter 5).

Contact lenses will be dispensed and the insertion, removal, and care training will occur during Visit 2, one week after the initial visit. All subjects are measured every six months for three years. The pupils are dilated and a comprehensive eye examination is performed annually, at Visits 1, 5, 7, and 9.

Subject Identification Number

When the parent of a subject signs the Parental Permission Form, the subject will receive his or her subject identification (ID) number. The number consists of two parts:

- subject number that starts from 1001
- subject initials.

For example, subject ID "1004–TJ" is the fourth subject enrolled and the subject's initials are TJ.

Ineligible subjects due to low myopia can return for a second screening visit after sufficient time to potentially warrant myopia progression. When they return, they will be given a new subject identification number (do not issue the previous number).

Visit Windows

Visit windows are the time period during which a subject should be examined. The date of visits 2-9 are scheduled based on the date of baseline visit. All attempts should be made to examine the subject as early in the window as possible in case the subject needs to re-schedule to a later date. In order to facilitate coordination of scheduling and to set reminders, the next appointment should be made upon completion of the current appointment, even if it does not occur for six months. The visit windows are shown in Table 7-2.

Table 7-2: Visit windows for the BLINK Study.

Visit	Target Window (Day)	Acceptable Window (Days)
2	7	4-10
3	21	14-28
4	180	150-210
5	365	335-395
6	545	515-575
7	730	700-760
8	910	880-940
9	1,095	1,065-1,125

Some children may require multiple visits to learn insertion and removal of contact lenses. The subsequent visits should be scheduled as early as possible, so that Visit 3 can occur within the visit window, but after one week of wear.

Unscheduled Contacts and Visits

Subjects will have the telephone and/or pager number of the clinic PI and clinic study coordinator. If the call involves such things as the scheduling of visits or other aspect of study operations, the PI will address those questions as appropriate. If these calls involve eye care matters, the PI will be contacted to examine the subject. If it appears that the subject has experienced an event in which medical care may be indicated, study personnel will ensure that appropriate care is obtained by the subject.

The Unscheduled Visit Form should be completed, and an event report and/or adverse event form from the local IRB should be completed if necessary.

Recruitment

Recruitment methods may include, but are not limited to direct mailings to potential subjects who are likely to meet entry criteria, newspaper and/or radio advertisement, recruitment brochures, and social media. Preliminary determination of eligibility will be made during the first contact, whether in person or over the telephone. Final eligibility will be determined at the 3-week Visit after the 2-week run-in period for compliance with atropine (see details in Chapter 5).

The goal is to complete recruitment as quickly as possible. Every effort should be made to complete enrollment before the one-year deadline. The recruitment methods most likely to result in numerous visits should be utilized first. However, not all methods should be incorporated at one time because a large bolus of potential subjects could result in scheduling one to two months in advance. A new recruitment effort should be conducted as the last one to two weeks of baseline examinations are being conducted. When submitting the original IRB approval, include as many potential recruiting methods as possible because approval of amendments for recruitment may require several weeks.

Discontinuation

As a tenet of the informed consent process, subjects are able to withdraw from a study at any time. If a subject does not want to wear contact lenses, the subject should be asked why s/he does not want to wear contact lenses and every effort should be made to alleviate the reason for discontinuation. The subject and parent should be reminded of the importance of continuing in the study and reminded of the free comprehensive eye examinations and glasses

throughout the study. At each follow-up visit, the subject should be asked if s/he would like to resume contact lens wear.

Subjects have the right to withdraw participation in a study at any time, but losses to follow-up may significantly affect the validity of the study. Every effort should be made to retain every subject for the entire study, including subjects who are difficult to schedule, subjects who are very demanding, and subjects whom you simply do not like.

If a subject moves from the area, the project may allow paying for the subject and one adult to fly to an appointment, one night's stay in a hotel, and ground transportation. The total reimbursement should not be greater than $1350 per visit. This decision will be made on a person-by-person basis by the PI. If a subject cannot be located, and all potential contacts have been exhausted, the PI will conduct a professional search using alternative resources.

If a subject wishes to discontinue and all alternatives have been discussed, the examiner should ask the subject if he or she would come back for Visit 9 only. If the subject agrees to return for the last visit, then he or she is not a loss to follow-up, and the Discontinuation Form should not be completed. If the subject refuses to attend all of the remaining visits, the Discontinuation Form should be completed. At this time, complete the discontinuation section of the Study Completion Form in REDCap. Ask the subject if it would be acceptable to continue sending them information and see if it would be okay to call them before the last visit to determine whether the subject changed his or her mind.

Chapter 8: Informed Consent

Introduction

Clear explanation of the study, and answering all questions is not only required but also fosters good compliance and reduces the number of drop-outs and subjects who cross-over.

Study Population

The subject sample in the clinical study will be myopic children between the ages of 7 and 11 years. During the informed consent process, we will explain the subjects' rights, including voluntary participation, freedom to discontinue participation, and those decisions will not affect the quality of the health care available to them at that institution.

Data Management and Confidentiality

All data entered are identified with subject number only. All data will remain confidential, and no subjects will be identifiable from reports generated for this research. Identifiable personal information will remain at the clinic centers. All subjects will receive a Notice of Privacy Practices, either as a separate document or as part of the informed consent document.

Subjects Visits

Subjects will be asked to take part in the following visits (visit length is in approximation):

Visit 1 (2.5 to 3.0 hours): informed consent, comprehensive vision examination, visual acuity, pupil size measurement, slit lamp examination, axial length measurement, videophakometry, cycloplegic autorefraction, peripheral autorefraction with and without the contact lens, peripheral eye length measurement, completion of surveys, and contact lens fitting.

Visit 2 (1.0 to 1.5 hours): slit lamp examination and insertion, removal, and care training.

Visit 3 (1.0 to 1.5 hours): visual acuity, slit lamp examination, accommodative lag, pupil size measurement, and surveys.

Visits 4, 6, and 8 (1 hours): slit lamp examination, visual acuity, pupil size measurement, and completion of study surveys.

Visits 5, 7, and 9 (2.5 to 3.0 hours): comprehensive vision examination, visual acuity, pupil size measurement, slit lamp examination, axial length measurement, videophakometry, cycloplegic autorefraction, peripheral autorefraction with and without the contact lens, peripheral eye length measurement, pupil size measurement, accommodative lag, and completion of surveys.

Risks and Benefits

Potential risks are minimal. A subject and his or her parents may feel inconvenienced by being asked to devote time and/or travel to the clinical site. Subjects' pupils will be dilated at the baseline visit and each annual examination. As a result of being dilated, subjects will be light sensitive and their near vision will be blurry. Subjects will be given disposable sunglasses to alleviate light sensitivity and they can remove their correction to see clearly at near during cycloplegia. One-out-of-every-three subjects will receive the control contact lens modality. Daily wear soft contact lenses have a corneal ulcer rate of approximately 1/2000 per subject-year (MacRae et al. 1991). The concentration of the 0.01% atropine eye drops to be used in this study is 100 times lower than the 1% atropine eye drops that have been widely used in other studies and proven to be safe (The Pediatric Eye Disease Investigator Group 2002; Chua et al. 2006; Chia et al. 2012; Repka et al. 2014).

All subjects will receive free comprehensive eye care, reduced cost for glasses, eye drops, and free contact lenses and contact lens supplies throughout the study. The information gained from this study will provide the eye care community with further knowledge about the potential myopia control benefits of combination treatment of low dose atropine and soft bifocal contact lens wear for children, and about the mechanism of the potential treatment effect, which will lead to improved myopia control products and potential myopia prevention products. The risks appear to be small in relation to the potential benefits.

Subject Selection

Our study sample will include subjects of both genders, and all racial and ethnic groups are eligible. We will recruit from Columbus, OH which will provide a representative sample of young myopes.

Chapter 9: Visual Acuity

Eyes

OD, OS, and OU at Visit 1 and OU at Visits 3-9

Equipment

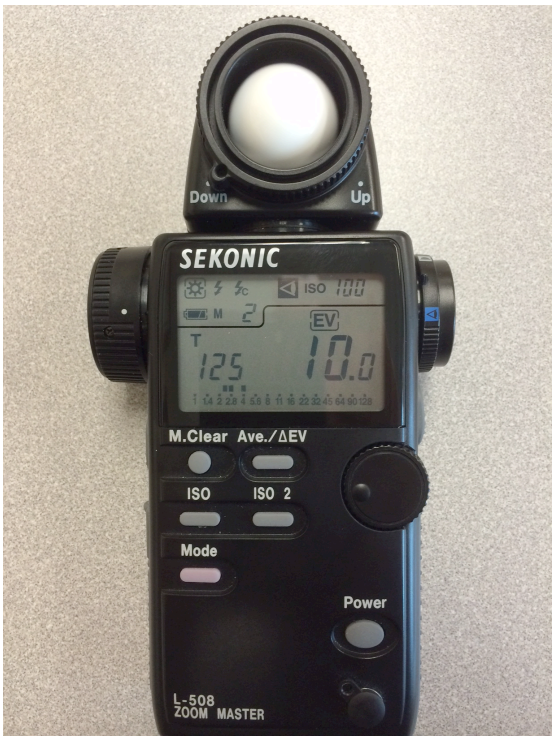
Bailey-Lovie logMAR high contrast charts #4 and #5, and low contrast visual acuity chart #6 (UC Berkeley School of Optometry, Berkeley, CA) are used. Test distances of 6 meters, 4 meters, and 2 meters must be clearly marked. The Sekonic L-508 Zoom Master (Sekonic, Tokyo, Japan) light meter will be used.

Chart Calibration

The chart should be calibrated to 9.3 to 9.9 EV (75 to 120 cd/m^2). If the number is below 9.3, more light is needed. If the number is above 9.9 less light is needed. There may be slight differences in instructions for each model of light meter, but the general calibration protocol follows.

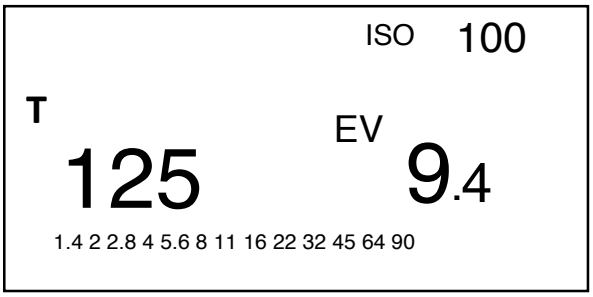
1. Press the [Power] button, and the LCD display will illuminate.
2. Turn the lens knob on the left of Figure 9-1 to the smallest white spot.
3. Turn the eye piece on the right so the pointer points to the blue square (Figure 9-1).
4. Turn the knob on the right, below the LCD display, until 125 appears in the lower left of the screen (Figure 9-1).
5. The number 100 should be displayed on the top, right (Figure 9-1).
6. Point the white orb on the top of the meter to you (Figure 9-1).

Figure 9-1: Sekonic light meter.



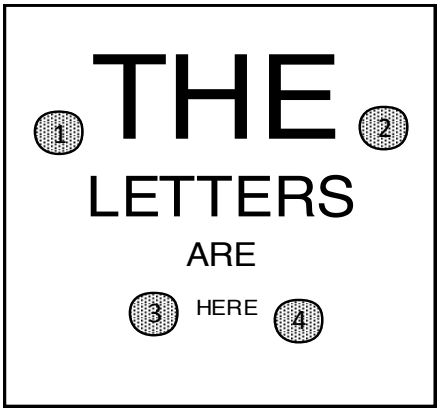
At this point, the LCD display should look like Figure 13-2, except the number to the right of EV may not be 9.4 (it can be anything at this point).

Figure 9-2: Light meter display.



7. Position yourself approximately 3-6 inches from the letter chart without blocking the illumination falling on it.
8. Look through the eyepiece, and point the light meter to area 1, as shown in Figure 13-3.
9. Press the button below the eye piece, and evaluate the number next to EV. This number should be between 9.3 and 9.9, inclusive.
10. Repeat steps 8. and 9. for each of the four areas.

Figure 9-3: Areas for visual acuity chart lighting calibration.



Once all four numbers are within the appropriate range, log them in the Visual Acuity Calibration Log. The visual acuity charts should be calibrated prior to the first subject examined, then monthly or every time the lights primarily lighting the visual acuity charts are moved.

Vision Correction and Specific Chart

Visual acuity (high contrast, low contrast, and near) is measured with manifest refraction in a trial frame and with +2.50 D add contact lenses (high contrast only) at baseline, in order to determine eligibility. At all subsequent visits, visual acuity (high contrast, low contrast, and near) is measured with both eyes while wearing habitual contact lenses with the spherical over-refraction in a trial frame. The eye(s), refractive correction worn, and chart are listed on the Visual Acuity Visit 1 Form and Visual Acuity Visits 3 – 9 Form.

High and Low Contrast Protocol

The following steps should be followed when measuring high contrast and low contrast visual acuity. If a subject attends a visit without his or her contact lenses, the subject should insert the contact lenses last dispensed.

1. Stand the subject at the mark located 4 meters from the chart.
2. Instruct the subject to read the first letter on each line, continuing down the chart until the first letter is missed.
3. Start two lines above the missed letter.
4. Tell the subject to read five letters from every line. If the subject misses a letter on the first line, then continue up the chart until the subject reads all five letters correctly.
5. Advise the subject to read slowly and to keep his or her head as still as possible. The pace should not be faster than about one letter per second.
6. The subject should not guess the next letter until s/he gives a definite response. The subject must guess a single letter. Once the subject read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response before guessing the next letter, then the change should be accepted.
7. Record the subject's answers on Visual Acuity Visit 1 Form or the Visual Acuity Visits 3 – 9 Form. Letters read correctly are marked with a slash through them, and letters read incorrectly are circled. If all the letters on a row are read correctly, you can draw a horizontal line through all five letters. Write the number of letters read correctly on each row. The subject continues reading down the chart to the last letter of each line until s/he misses 3 or more letters on a given line. Visual acuity testing for an eye is complete when the subject has reads the last letter of the line with 3 or more incorrect letters in that line.
8. If a subject gets 3 or more correct on the bottom line, move the subject to 6 meters and repeat steps 2 through 8.
9. If a subject does not get all five letters correct on the top line, move the subject to 2 meters and repeat steps 2 through 8.
10. Tally the total number of letters read correctly and mark the final test distance for each visual acuity measurement.

High Contrast Monocular Visual Acuity at Baseline

All high and low contrast distance visual acuity measures follow the protocol above, except for measurement of monocular (right and left eye) high contrast visual acuity with the manifest refraction in a trial frame.

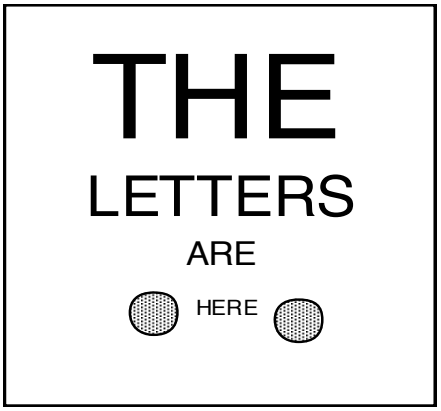
1. Stand the subject at the mark located 4 meters from the chart.
2. Instruct the subject to read the first letter on each line, continuing down the chart until the first letter is missed.
3. Start two lines above the missed letter.
4. Tell the subject to read five letters from every line. If the subject misses a letter on the first line, then continue up the chart until the subject reads all five letters correctly.
5. Advise the subject to read slowly and to keep his or her head as still as possible. The pace should not be faster than about one letter per second.
6. The subject should not guess the next letter until s/he gives a definite response. The subject must guess a single letter. Once the subject read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response before guessing the next letter, then the change should be accepted.
   - 6a. The subject continues down the chart in this manner until s/he reaches the 4.8 meter (16 foot) "R Z U F N" row of letters OD and "D H E V P" row OS, one line below the row of letters with a single, dark line to the right and left of the letters (or any line below that if the starting point for reading a line of letters is further down the chart.
   - 6b. Before the subject begins to read that line, place an 8.5 X 11 sheet of white paper on the chart to cover the letters below the line being read. If the subject reads three or more of the letters correct, move the paper down to reveal the next line of letters.
   - 6c. Repeat 6b. until the subject reads fewer than three letters correctly on a given line.
7. Record the subject's answers on Visual Acuity Visit 1 Form or the Visual Acuity Visits 3 – 9 Form. Letters read correctly are marked with a slash through them, and letters read incorrectly are circled. If all the letters on a row are read correctly, you can draw a horizontal line through all five letters. Write the number of letters read correctly on each row. The subject continues reading down the chart to the last letter of each line until s/he misses 3 or more letters on

a given line. Visual acuity testing for an eye is complete when the subject has reads the last letter of the line with 3 or more incorrect letters in that line.
8. If a subject gets 3 or more correct on the bottom line, move the subject to 6 meters and repeat steps 2 through 8.
9. If a subject does not get all five letters correct on the top line, move the subject to 2 meters and repeat steps 2 through 8.
10. Tally the total number of letters read correctly and mark the final test distance for each visual acuity measurement.

Near Visual Acuity Protocol

1. Ask the subject to hold the card in one hand and the bead in the other.
2. Tell the subject to place the bead at the lateral canthus and pull the chart away until the string is extended.
3. Turn on the stand lamp and point it at the near point card.
4. Point the light meter at either one of the shaded areas in Figure 9-4.
5. Press the button below the eye piece.
6. Determine whether the reading is within 9.3 to 9.9 EV. If so, measure visual acuity. If it is below 9.3, move the stand lamp closer. If it is above 9.9, move the stand lamp further away.
7. Instruct the subject to read the first letter on each line, continuing down the chart until the first letter is missed.
8. Start two lines above the missed letter.
9. Tell the subject to read five letters from every line. If the subject misses a letter on the first line, then continue up the chart until the subject reads all five letters correctly.
10. Advise the subject to read slowly and to keep his or her head as still as possible. The pace should not be faster than about one letter per second.
11. The subject should not guess the next letter until s/he gives a definite response. The subject must guess a single letter. Once the subject read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response before guessing the next letter, then the change should be accepted.
12. Record the subject's answers on Visual Acuity Visit 1 Form or the Visual Acuity Visits 3 – 9 Form. Letters read correctly are marked with a slash through them, and letters read incorrectly are circled. If all the letters on a row are read correctly, you can draw a horizontal line through all five letters. Write the number of letters read correctly on each row. The subject continues reading down the chart to the last letter of each line until s/he misses 3 or more letters on a given line. Visual acuity testing for an eye is complete when the subject has reads the last letter of the line with 3 or more incorrect letters in that line.
13. If a subject gets 3 or more correct on the bottom line, record the total number of letters read correctly to that point.
14. Record the number of letters read correctly and the test distance in REDCap.

Figure 9-4: Areas for near visual acuity chart lighting calibration.



Spherical Over-Refraction

The spherical over-refraction should be performed while the subject is wearing his/her habitual contact lenses. If the subject does not wear contact lenses to the appointment, the last lenses prescribed should be provided to the patient to wear during the beginning of the examination.

1. Use trial lenses to over-refract the subject.
2. Occlude the left eye.
3. Obtain Snellen visual acuity, pushing the subject to guess difficult letters.
4. Push plus, and only add minus power if the visual acuity improves.
5. Occlude the right eye and open the left eye.
6. Repeat steps 3. and 4. for the left eye.
7. Place the over-refraction results in a trial frame and test the visual acuity.

Contact Lens Power Change

A new contact lens power may be provided if the over-refraction exhibits a change of ≥–0.50 D, or if it is deemed to be clinically necessary to improve vision.

Chapter 10: Modified Thorington

Equipment

The Muscle Imbalance Measure (MIM) near card (Bernell Corporation, South Bend, IN) will be used to measure near phoria. All near measurements take place at 40 cm.

Introduction

Near phoria has been shown to be related to the myopia control treatment effect with bifocal or multifocal spectacles, so we will measure the near phoria of all subjects at Visit 1 (baseline) through the manifest refraction, at Visit 3 with the study contact lenses, and at Visits 5, 7, and 9 with the study contact lenses. We will use Modified Thorington to measure the near phoria because it is simple for children to understand, and it is highly repeatable (Rainey et al. 1998).

In addition to the modified Thorington technique at near to assess the near phoria, unilateral and alternate cover test will be performed at distance (to assess distance binocularity), and unilateral cover test will be performed at near (to check for near strabismus). When performing cover test at distance and near, the child fixates on a target two lines above best-corrected visual acuity.

Order of Testing

The primary interest is the near phoria so that protocol is presented first. However, use the following order for testing:

1. Unilateral cover test (UCT) at distance
2. Alternate cover test at distance (ACT)
3. UCT at near
4. Near phoria using Modified Thorington technique (near MIM card)

Modified Thorington Protocol

Necessary Equipment

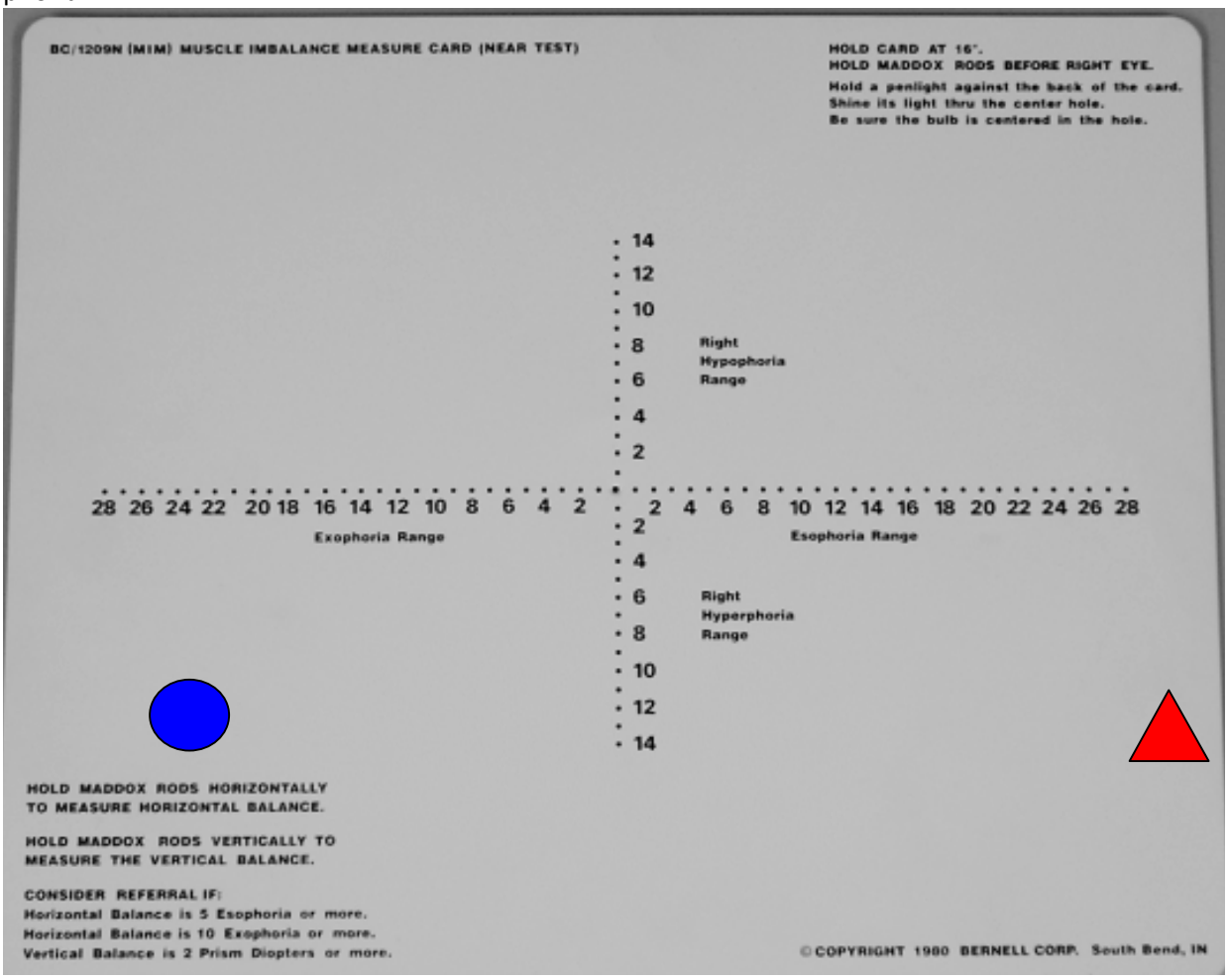
- Maddox Rod
- Muscle Imbalance Measure (MIM) near card
- Pen light

Lens Correction

- Manifest refraction at Visit 1
- Habitual contact lenses at Visits 3, 5, 7, and 9

1. Have the child hold the Maddox rod horizontally in front of the right eye for 30 seconds before testing to encourage dissociation and to allow for manifestation of the full phoria.
2. Hold the near Muscle Imbalance Measure (MIM) card at 40cm from the child (Figure 10-1).
3. While the child is encouraged to keep the letters and numbers on the card clear, hold a pen light behind the card and shine it through the hole in the center of the card.
4. Have the child state whether the red line they see is on the side of the red triangle (esophoria) or the blue circle (exophoria). Have the child tell you the number the line goes through. Note that the card is marked with even numbers only. If a child states that the line is between two even numbers, record the number between these numbers (for example, if the line is between the 2 and the 4 on the right side of the card, record 3pd esophoria).
5. Record the finding using a positive sign (+) to indicate **eso** deviations and a negative sign (–) to indicate **exo** deviations.

Figure 10-1: Near Muscle Imbalance Measure (MIM) card for the modified Thorington Technique of measuring near phoria.



Cover Test Protocol

Materials

- Parrot stick (for near UCT)
- Visual acuity chart (for distance UCT and ACT)
- Cover paddle

Distance and Near Unilateral Cover Test (UCT)

Unilateral cover test will be used to ensure that a tropia is not present at distance or at near.

Procedure

1. Have the child fixate on a letter two lines above threshold on the target, depending on whether distance or near testing is being performed.
2. Use an opaque cover paddle to cover the right eye. Watch the left eye as the right eye is covered. Movement of the eye not being covered indicates a tropia is present. (Note: presence of a tropia at enrollment disqualifies the subject.)
3. Use an opaque cover paddle to cover the left eye. Watch the right eye as the left eye is covered. Movement of the eye not being covered indicates a tropia is present.
4. If a movement is seen initially without any prism (i.e., a tropia is present), this movement should be assessed for the direction and approximate amount of movement (in prism diopters).

5. If no movement is present on UCT, the subject may have a phoria. At distance, proceed to the Alternate Cover Test to determine the direction and magnitude of the distance phoria, if present. (At near, use the Modified Thorington technique to determine the direction and magnitude of the near phoria.)
6. Place a prism over the eye that is deviated. The orientation of the prism base should match the direction of the eye movement observed on the unilateral cover test (Table 10-1). Take care not to tilt or rotate the prism. The prism should be held close to the eye (spectacle plane).

Table 10-1: Prism neutralization of eye movement during the alternate cover test.

Movement seen	Direction of deviation	Prism orientation
Outward	Eso	Base Out (BO)
Inward	Exo	Base In (BI)
RE down & LE up	Right hyper or Left hypo	Base Down over RE or Base Up over LE
RE up & LE down	Left hyper or Right hypo	Base Up over RE or Base Down over LE

7. Place the occluder over the prism. Shift the occluder to the opposite eye, observing the movement of the deviating eye through the prism. If the eye still moves in the same direction as before, increase the amount of the prism. Keep increasing the prism until no movement is observed through the prism. Then continue to increase the prism until the direction of eye movement is reversed from what was seen initially (this is "reversal"). Note the prism amount prior to reversal.

Distance Alternate Cover Test (ACT)

ACT is only performed at distance to determine the magnitude and direction of a phoria. Use the Modified Thorington technique to determine the phoria at near.

Procedure

1. While the child maintains fixation on the target, introduce the cover paddle over the left eye. Once the occluder is placed over the left eye, the occluder should always be covering an eye until the endpoint is reached to maintain dissociation.
2. Move the occluder to the right eye, observing the left eye for any movement as the left eye is uncovered.
3. Move the occluder back to the left eye, observing the right eye for any movement as the right eye is uncovered. (Note: Move the paddle briskly between the left and right eyes to ensure complete dissociation; however, hold the paddle in front of each eye long enough to allow time for re-fixational movements before changing paddle position.)
4. If movement is seen without any prism, assess the movement for direction and approximate magnitude (in prism diopters) as described in UCT steps 5 and 6 above until reversal is achieved.

Recording UCT and ACT

Record the high neutral finding, defined as the last (highest) prism power that induced no movement before you saw "reversal" of the movement.

Example

Esotropia that is still eso with 10 BO in front of OD, neutral with 12 BO, but reverses with 15BO.

Based on the movement seen, estimate the high neutral. For example, if there is a significant reversal of movement with 15 BO, record 12 BO; if there is very little reversal movement with 15 BO, record 14 BO.

Chapter 11: Accommodative Lag and Peripheral Defocus With Contact Lens at Near

Eyes

OD

Reason for Measuring Accommodative Lag

Accommodative lag has been shown to be related to the myopia control treatment effect with bifocal or multifocal spectacles. We will measure the accommodative lag of all subjects using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL) at Visit 3 (the 3-week visit) and annually (Visits 5, 7, and 9).

Measurements will be made at 33cm (3-D demand). The letter target used is 2.06 M in size (20/125 Snellen Equivalent). This letter size is used because it approximates text size in materials read by children in this age group.

Reason for Measuring Peripheral Defocus With Contact Lens at Near

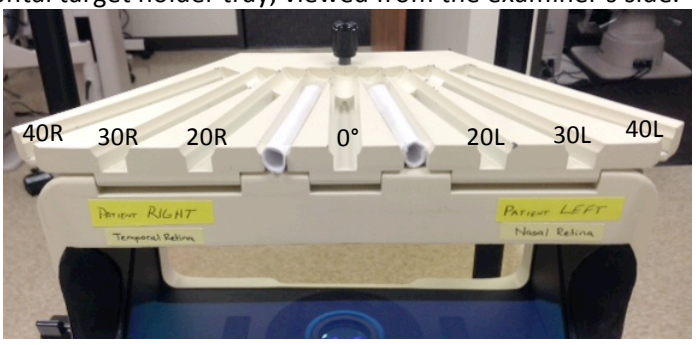
Peripheral defocus at near may play a role in the regulation of eye growth. We will measure the optical defocus while wearing the contact lens in order to evaluate the role of peripheral vision during accommodation in regulating eye growth. It will be measured using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer. Peripheral defocus with the contact lens at near is obtained at the same time points as accommodative lag.

All Grand Seiko settings and laptop computer settings are the same as noted in the *Central Autorefraction* chapter. The Grand Seiko has been modified to allow for either a laser pointer or a near point rod to be placed centrally or out to 40° from the line of sight in 10° increments along the horizontal meridian. Measurements in the horizontal meridian will be made centrally (0°) and at ±30° from the line of sight. (Note: No measurements will be made at ±10°, ±20°, and ±40°, and these slots should be filled to prevent accidentally placing a target in these locations).

Measurement Procedure

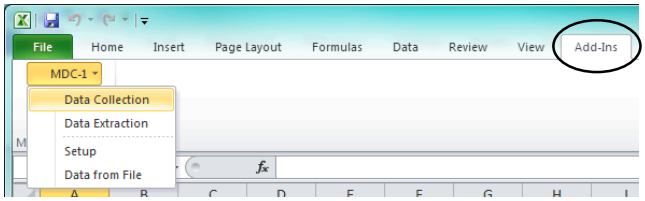
These measurements are performed on the right eye only with normal accommodation (i.e., NO cycloplegia). Left and Right refer to the direction the subject looks. A picture of the autorefraction horizontal target holder tray (examiner side) is shown in Figure 11-1.

Figure 11-1: autorefraction horizontal target holder tray, viewed from the examiner's side.



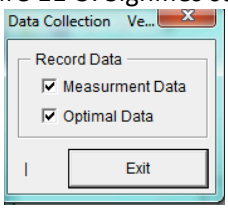
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated as COM3).
2. Navigate to the peripheral autorefraction Excel Template file (PeripheralAuto_Template.xltx) located in the "BLINK Templates" folder on the desktop and open the file.
3. Once Excel opens the template, click the "Add-Ins" tab in the ribbon and click "MDC-1" and select "Data Collection" (Figure 11-2).

Figure 11-2: Click on the Add-Ins tab in Excel.



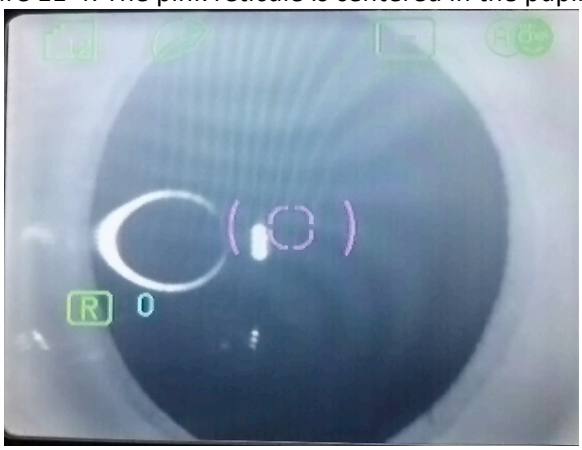
4. Once the Grand Seiko successfully connects to the laptop, you will see the window in Figure 11-3.

Figure 11-3: Signifies successful connection to laptop.



5. Place an eye patch over the subject's left eye.
6. Place the subject's chin on the chinrest. The forehead rest is not used for horizontal measurements because it prevents accurate instrument focusing during measurements. It may be necessary to have assistance holding the subject's head in place during measurements.
7. Place the 33cm near rod in the appropriate slot to measure with the subject looking 30° to his/her left (nasal retina). *Verify that the target is located at the 33cm mark on the rod!*
8. Tell subject to keep looking straight ahead with eyes, but to turn head (guide with your hands) so that they are looking straight at the letter target located at 33cm on the near rod. Visually inspect to ensure that the subject's eyes are in primary gaze and the subject's head/nose is pointed directly at the letter target.
9. Obtain a view of the eye on the screen. For peripheral measurements, find the best iris focus by moving the instrument in or out. *Note: For peripheral measurements, the iris is used to focus (not the white keratometry circle).*
    - Exception: For central measurements *ONLY* (0°), the white keratometry circle should be in focus as shown in the *Central Autorefraction* chapter.
10. Center the pink reticule in the horizontal meridian and vertical meridian of the pupil. *Note: For peripheral measurements, do not center the pink reticule in the center of the white keratometry circle reflecting off the cornea!* An example showing correct horizontal centration for a *peripheral measurement* is shown below.
    - Exception: For central measurements *ONLY* (0°), the pink reticule is centered within the white keratometry ring as shown in the *Central Autorefraction* chapter (Figure 11-4).

Figure 11-4: The pink reticule is centered in the pupil, not the white keratometry ring during peripheral autorefraction.



11. Encourage the child to keep the letters as clear as possible. Have the child focus on a different specific letter on the target at each measurement location to ensure the child is attentive and accommodating.
    (Important: Constantly remind the child to keep the letters clear when taking measurements!)
12. Obtain at least five "good" readings in which neither the sphere nor cylinder differ from the median by more than 1.00 D. When in doubt, take additional measurements to ensure that at least 5 "good" measurements exist.
13. Press Print and tape the printout in the location indicated on the exam form.
    (Important: Remember to press the print button between each change in gaze!)
14. Repeat steps 8 through 13 with the near rod located at Central (0°) and 30° Right (30R).
    (Note: It is important that you always follow this order – 30L, Central, 30R. If you ever accidentally go in a different order, this must be noted in the Excel file once measurements are complete.)

15. When finished measuring the horizontal meridian, click the "Exit" button on the laptop to end the connection between the Grand Seiko and laptop.
16. Save the Excel file in "Documents" in the "BLINK Data" folder using the following file-naming scheme:
    SubjectID-CLNear-Horiz-VX (where X is the visit number) – Ex: 204-TJ-CLNear-Horiz-V1.xls
17. Upload the horizontal data file to subject's record using REDCap.

Chapter 12: Slit Lamp Examination

Eyes

OD and OS

Equipment

Any slit lamp biomicroscope can be used for the slit lamp examination. Anomalies will be graded using the Efron Grading Scales (Efron N. Grading scales for contact lens complications. Ophthalmic Physiol Opt 1998;18:182-6).

Protocol

All observations should be made after contact lens removal.

The following anomalies will be graded from 0.0 (normal) to 4.0 (severe) in 0.1 increments according to the Efron Grading Scales:

- Conjunctival redness
- Limbal redness
- Corneal neovascularization
- Corneal staining
- Papillary conjunctivitis
- Blepharitis
- Meibomian gland dysfunction
- Corneal infiltrates

The general interpretation of each grading step is shown in Table 16-1. All grades of 3 or higher trigger an adverse event report, but grades less than 3 may also trigger an adverse event report if deemed clinically necessary.

Table 16-1: Interpretation of grading scale.

Grade	Severity	Clinical Interpretation
0	Normal	Clinical baseline reference
1	Trace	Clinical attention not required
2	Mild	Clinical action may be required
3	Moderate	Clinical action usually required
4	Severe	Clinical action certainly required

Fluorescein Instillation

Fluorescein should be instilled after all slit lamp observations except corneal and conjunctival staining have been conducted.

1. Place one or two drops of Biotrue on the end of the fluorescein strip.
2. Tell the subject to look down and pull up the top lid.
3. Place the flat end of the strip on the conjunctiva, but do not wipe across the conjunctiva.
4. Use a cobalt blue filter and a yellow Wratten #12 barrier filter to observe the corneal and conjunctival staining.

Contact Lens Movement, Centration, and Push-Up

Each of these measures should be assessed with white light, while the subject's eyes are in primary gaze. Each assessment is categorized accordingly:

- Contact lens movement
  - Extremely inadequate (no movement)
  - Slightly inadequate (<0.2 mm upon blinking)
  - Optimum (0.2-0.4 mm upon blinking)
  - Slightly excessive (0.4-1.0 mm upon blinking)
  - Extremely excessive (>1.0 upon blinking)

- Contact lens centration
  - Optimum (symmetric about center of cornea)
  - Slightly decentered (no limbal exposure)
  - Extremely decentered (limbal exposure)
- Contact lens push-up
  - Excessive, unacceptable
  - Moderate, acceptable
  - Optimum
  - Minimal, acceptable
  - Insufficient, unacceptable

Chapter 13: Pupillometry

Eyes

OD

Equipment

Measurement of pupil diameter is performed using the NeurOptics VIP-200 Pupillometer (NeurOptics, Inc., Irvine, CA) prior to the instillation of any mydriatic or cycloplegic drops while the subject is uncorrected. The objective of the measurement is to estimate the habitual pupil size. Measurements should be performed at Visits 1, 3, 4, 5, 6, 7, 8, and 9.

For the mesopic condition, the subject should stand facing the examiner with his or her back toward the wall-mounted visual acuity chart. The room lights should be off except for the incandescent lamp over the examination chair at the opposite end of the room, which should be pointed straight down toward the examination chair.

For the photopic condition, the subject should stand facing the examiner with his or her back toward the wall-mounted visual acuity chart, and the visual acuity chart illumination should be turned on and be the same as when taking visual acuity measurements (approximately 75 – 120 cd/m^2 or 9.3-9.9 EV; see Chapter 13).

Procedure

1. With the lights in the photopic condition, pull the pupillometer forward and then up to release the unit from the charging base.
2. Power On if needed by holding an arrow key down for at least three seconds until a beep tone is heard.
3. Press the OD button to activate the unit.
4. Confirm that the date and time in lower right portion of the screen are correct. (If incorrect, press the Down arrow, then the Right arrow to put the green square over the Tools icon (nut and bolt). Press the middle Select button, then the Down arrow key to Change Date/Time. Using the directional Arrow keys, Clear any incorrect entries and key in the correct date and/or time. All navigation on the menu bars is done using the directional Arrow keys.
5. Enter the subject ID number. Press the Down arrow key, then the Right arrow key to place the green square over the Folder icon. Press the Select center button, then the Down arrow key to Enter ID. Press the Select center button and enter the subject's numeric ID number. Press the OD button to exit to a measurement of the right eye.
6. Bring the unit up in front of the subject's right eye with the eye cup resting against the subject's face and hold down the OD button continuously.
7. When the pupil is marked with a green circle, release the button to initiate the measurement. Hold the unit still during the few seconds of the measurement. Take care that the eyelids do not cover the pupil.
8. If the green measurement circle was not centered over the pupil, delete the measurement by using the Eraser icon at the right side of the three-icon Tool menu. Repeat the measurement until the green measurement circle is centered over the pupil.
9. Record the pupil size to the nearest 0.1 millimeter on the examination form.
10. Repeat steps 6-9 while the lights are in the mesopic condition.

Chapter 14: Choroidal Thickness

Eyes

OD

Equipment

The Spectralis OCT (Heidelberg Engineering, Carlsbad, CA) will be used to collect retinal OCT images that include the choroid. The instruments Enhanced Depth Imaging (EDI) mode will be utilized to maximize choroidal image quality.

Reason for Measuring

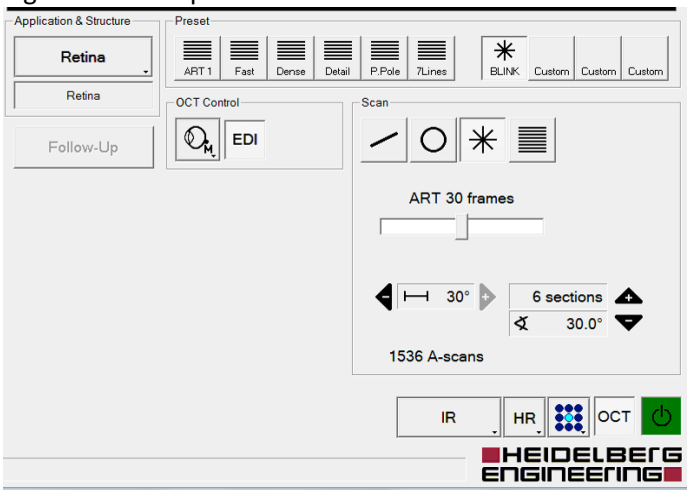
Studies have reported changes in choroidal thickness in response to optical defocus. We will investigate whether changes in choroidal thickness occur over in the control and treatment groups. OCT images will be collected through a non-dilated pupil. Because choroidal thickness changes have been reported to occur rather quickly when the eye is exposed to a change in defocus, all choroidal thickness measurements will be made immediately after removing the child's study contact lens from the right eye. Measurements will be made at Visits 2, 3, 5, 7, and 9.

One-time Instrument Setup

The BLINK scan parameters for the Spectralis can be programmed into one of the custom buttons on the acquisition screen. The following setting should be set and assigned to one of the custom buttons and labelled as "BLINK" to allow examiners to quickly set the scan parameters with one button click (Figure 14-1):

- Scan:
  - Star pattern
  - ART 30 Frames
  - A-scan width = 30 degrees
  - 6 sections
  - Section separation angle = 30 degrees
- OCT Control:
  - EDI mode ON
- HR Mode (High Resolution)
  - 1536 A-scans

Figure 14-1: Acquisition screen. Note the "BLINK" button on the top, right.



Procedure

1. Identify the subject by doing the following:
    a. At Visit 2: Click new patient icon and enter the following subject information, then click OK:
        Last name: BLINK
        First name: patient ID (Ex: 204-TJ)
        Date of birth: Enter 1 for the month, 1 for the day, and the subject's actual year of birth.
        Sex: Male or Female
    b. At all other Visits:
        1. Click the subjects ID on the left side of the window, which will make that ID appear on the right side of the window. (Only the ID of the subject to be measured should be on the right side of the window!)
        2. Click the re-examine button . A window will appear with the subject ID asking if you want to re-examine the subject.
        3. Verify that the correct ID is displayed and click Yes.
2. The "Examination Data" window will appear. Select the following:
    a. Device type: Spectralis OCT
    b. Operator: <*LEAVE BLANK*>
    c. Study: BLINK
3. After clicking OK, the "Eye Data" screen appears. No changes are necessary on this screen. Click OK.
4. The Spectralis imaging screen will appear. Once the red button on the bottom right of the touchpad (and also bottom right of the computer screen) turns yellow, press the yellow button to activate the OCT camera.
5. On the touch pad:
    a. Press the "IR + OCT" button on the left side (Figure 14-2a).
    b. Press the "More" button in the upper right corner. On the next screen, press the "Auto" button under the Image Brightness section (Figure 14-2b).

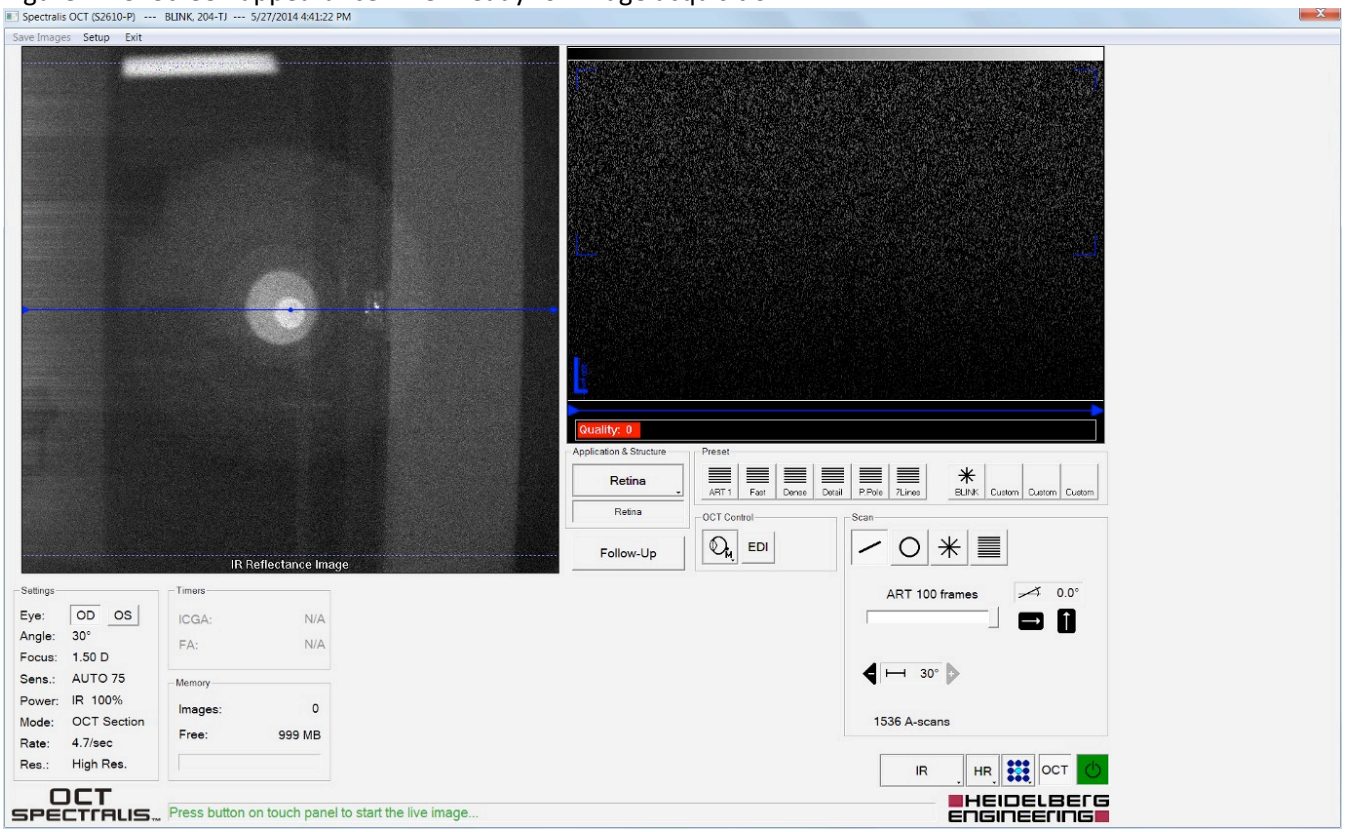
Figure 14-2: Touch pad buttons to push.

14-2a

14-2b

After completing these steps on the touch pad, the computer monitor will look as shown in Figure 14-3.

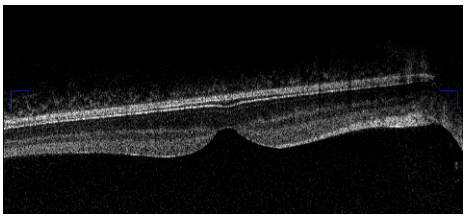
Figure 14-3: Screen appearance when ready for image acquisition.



6. Place an eye patch over the child's left eye
7. Place the child's chin in the chinrest and forehead against the forehead bar, and tell the patient to look straight ahead into the instrument at the blue light. (Hint: Tell the child to ignore the moving red light and to only look at the blue light.)
8. Look at the "IR Reflectance Image" window on the left of the screen, and align the OCT camera in front of the pupil (you will see a bright spot when you are in front of the pupil). Push the instrument forward until you have a full view of the retina in the left window with no dark corners. On the right side of the screen in the OCT window, you will see a retinal OCT image appear. When the retinal OCT image first appears, the image will be right side up (retina on top and choroid on bottom). Ensure the OCT image is centered vertically on the screen and that the bottom edge of the choroid avoids any faint reflections or ghost images seen at the bottom of the OCT image (see ghost image example shown later in Figure 14-10).

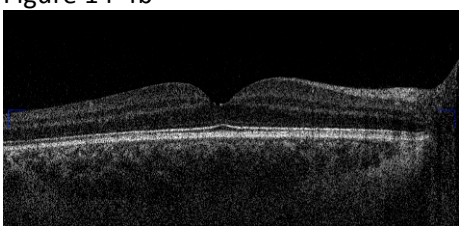
(Note: Moving in and out will adjust the vertical position of the OCT image. If you push in too far, the image flips so that the choroid is on top and the retina is on bottom; if this happens, pull the instrument back.)

Figure 14-4a



Upside down
(pull instrument back!!!)

Figure 14-4b



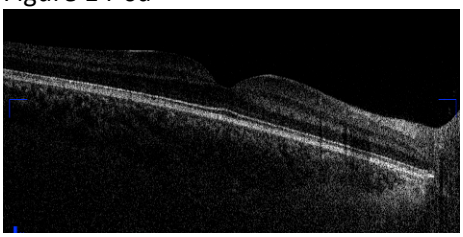
Correct orientation
Retina on top, choroid on bottom

9. Focus the IR Reflectance Image by turning the focus knob (Figure 14-5) on the OCT head counterclockwise (which adds plus) until it is blurry, and then clockwise (which adds minus) until the fundus image and vasculature in the IR Reflectance Image window first looks clear. Note: the focus amount should be about the same as the eye's refractive error. The focus value is displayed on the bottom left of the screen under the title "Focus."

Figure 14-5: Focus knob.

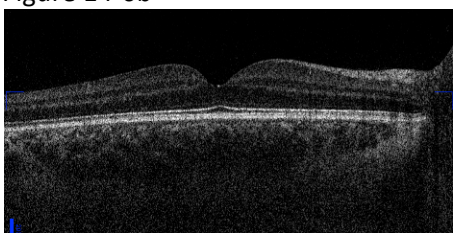
10. Move the OCT head left and right to flatten the OCT b-scan image AND until you have maximized image signal on the right and left side of the b-scan (Figures 14-6a-c). (Note: Very subtle tilting of the b-scan is sometimes needed to maximize image signal across the entire b-scan.) The bold blue line in the IR Reflectance Image window indicates the scan direction, which is currently horizontal. (Note: When scanning horizontally, moving the OCT head left and right allows you to flatten the OCT b-scan image.)

Figure 14-6a



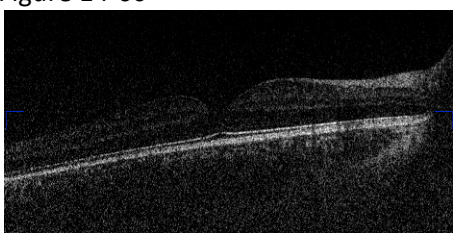
Not flat (tilted)
Image signal reduced on one side

Figure 14-6b



Flat (good)
Image signal uniform across b-scan

Figure 14-6c



Not flat (tilted)
Image signal reduced on one side

11. Click the button labelled "BLINK" in the Preset area (Figure 14-7). A star pattern will appear on the screen, and the instrument will now be scanning vertically. Flatten the OCT image again, this time by adjusting the OCT head up and down using the joystick. (Note: When scanning vertically, moving the OCT head up and down by rotating the joystick flattens the OCT b-scan image). The screen will look as it does below when properly aligned in the vertical dimension:

Figure 14-7: Preset area. Note the "BLINK" button below the right image (see arrow).

12. Be sure that the OCT b-scan image is centered vertically within the window and is flat with good image signal across the b-scan, and then activate the eye tracking mode:
    a. Visit 2: Activate the eye tracker by pressing the black gain control button (Figure 14-8) on the touch pad. (Note: If you engage eye tracking when the b-scan is not flat or when the full retina and choroid are not visible and centered vertically in the OCT b-scan window, you will not be able to acquire the images needed and part of the image will be cutoff. If this happens, turn off the eye tracker, get the OCT b-scan flat and centered vertically in the window, and reactivate the eye tracker.)

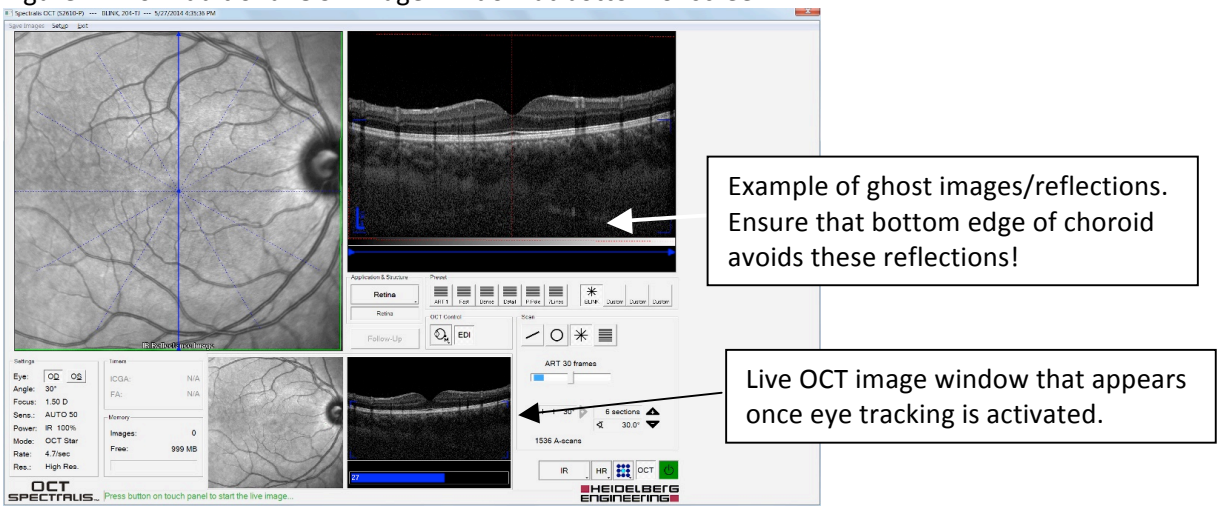
Figure 14-8: Note the round, black gain control button.

    b. All Visits after Visit 2: Click the "Follow-Up" button using the mouse. This mode maximizes instrument repeatability. Select the baseline image from reference examination the list (Figure 14-9, only one exam should be available to pick) and click OK. The eye tracker is now activated. (NOTE: If the "Follow-Up" button is grayed out, this means that a reference image was not set at Visit 2. See the "Setting the Reference Image" section below to set the reference image. The Follow-Up button will then be available.)

Figure 14-9: Click on the image shown to improve repeatability.

With eye tracking activated, you see an additional live OCT image window at bottom of screen (Figure 18-10)

Figure 14-10: Additional OCT image window at bottom of screen.



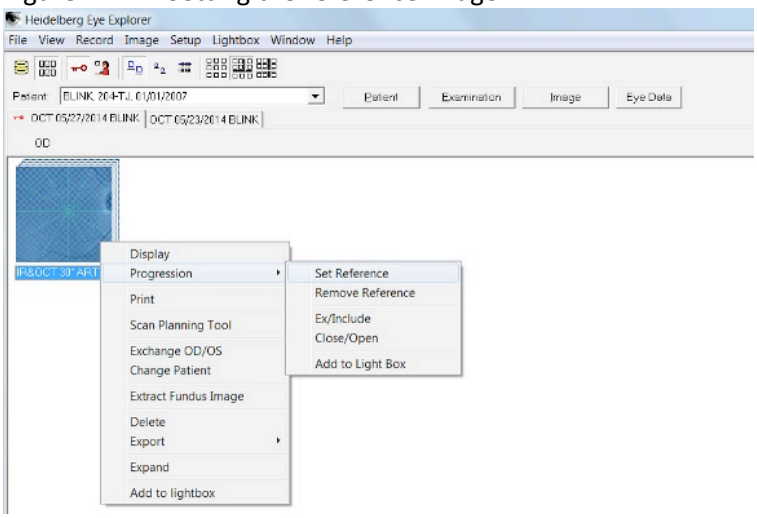
13. Watch the live OCT image at the very bottom of the screen throughout the scan acquisition to ensure proper alignment is maintained throughout the scan. When ready to begin the scan, press the "ACQUIRE" button on the touch pad. Maintain instrument alignment throughout the scan until all b-scans have been acquired.
    Acquisition Pearls:
    - It is OK for the subject to blink during the acquisition.
    - If the subject looks away, remind him/her to look at the blue light only and to ignore the red moving light.
    - Because the eye tracker is active, if the subject looks away, the scan will halt until the subject looks back and will then resume.
14. When acquisition is complete, click "Save Images" and then click "Exit" (both are on the upper left side of the screen.
15. Verify the quality of each b-scan by double clicking on the scan thumbnail and scrolling through the images. If there are images with poor quality (i.e., pixilated b-scans, b-scans with the choroid cut off, or b-scans that are severely tilted), repeat the scan following the steps above.
16. Upload E2E file to RedCAP. (See OCT export and upload section below.)

Setting the Reference Image

This should only be done at Visit 2 after saving the OCT images. Setting a reference image maximizes the repeatability of OCT images that are acquired at subsequent visits when using the "Follow-Up" mode. To set the reference image used in Follow-Up mode, do the following:

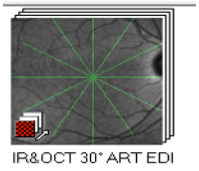
1. Select the best scan acquired at Visit 2 to use as the reference image. Right click on the baseline OCT scan thumbnail (Figure 14-11), select "Progression" and then select "Set Reference"

Figure 14-11: Setting the reference image.



2. A red and black square can now be seen in the bottom left side of the thumbnail (Figure 14-12) indicating that it is a reference image that can be selected when using Follow-Up mode at return visits.

Figure 14-12: Reference image.

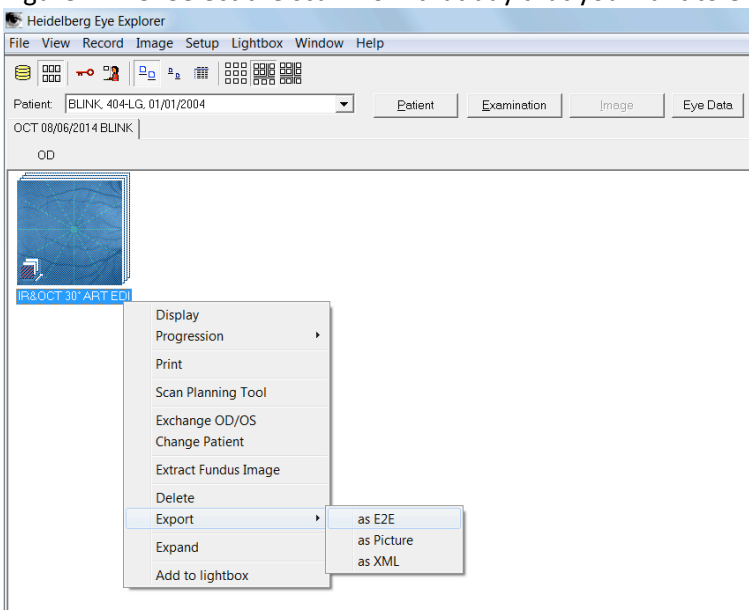


OCT Export and Upload

After each visit, the OCT images from that visit will be exported and uploaded to RedCAP using the following steps:

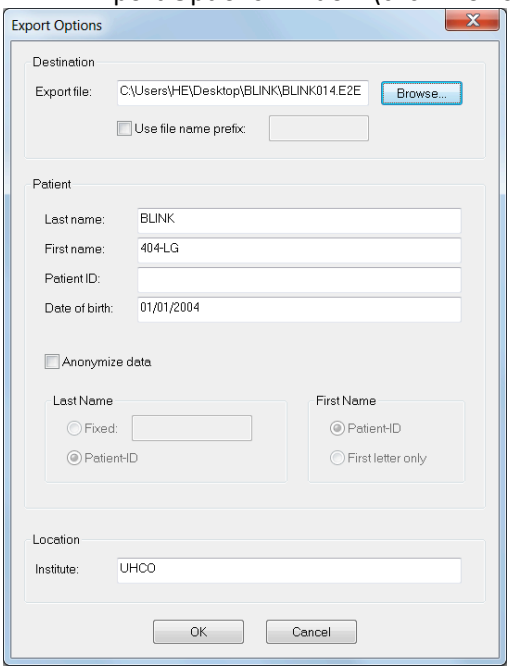
1. Select the OCT measurement from that day that had the best b-scan quality. Right-click and select “Export” and then “as E2E”.

Figure 14-13: Select the scan from that day that you want to export.



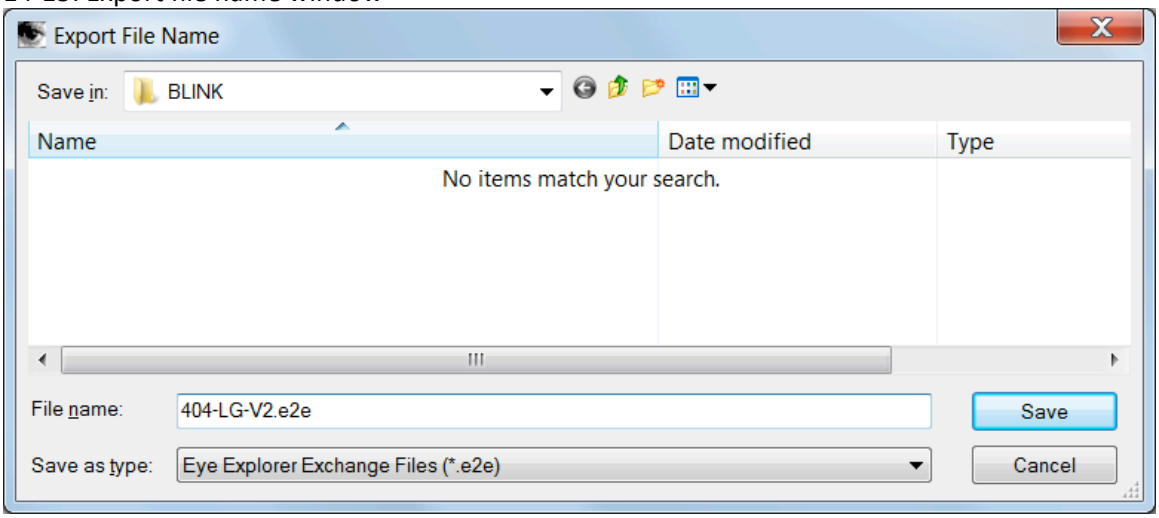
2. In the “Export Options” screen that appears, click the “Browse” button. (Do NOT click OK!) An “Export File Name” window will appear.

14-14: Export Options window (click Browse)



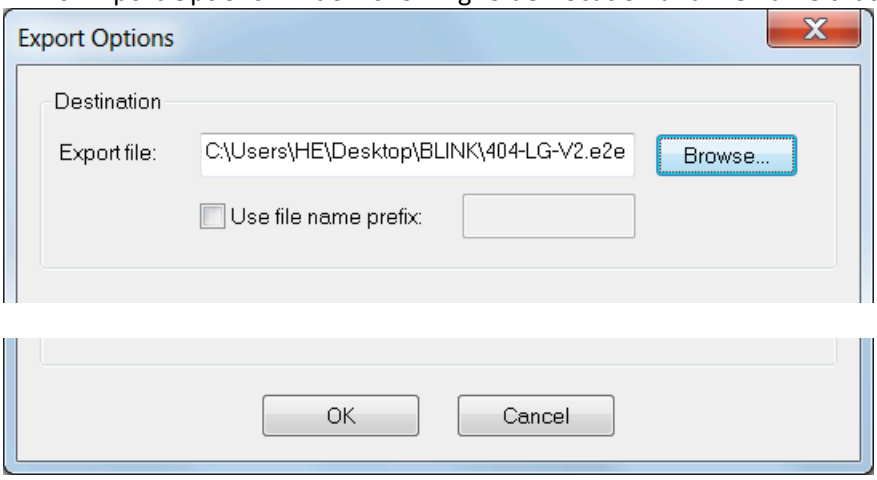
3. In the "Export File Name" window that appears, navigate to the folder where you want to save the exported file. In the "File name" field, name the file using the following file-naming scheme and click "Save":
   SubjectID-VX (where X is the visit number) - Ex: 404-LG-V2

14-15: Export file name window



4. In the "Export Options" window, you will now see that the "Export file:" field contains the folder location and file name that you specified in the previous window.

14-16: Export Options window showing folder location and file name that you entered in the previous step.



5. Click the "OK" button to complete the export. Now upload the exported E2E file in RedCAP.
   (Note: The file is large, and uploading to RedCAP will take a few seconds to complete.)

Chapter 15: Central Autorefraction

Eyes

OD and OS

Equipment

Autorefraction is conducted using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL).

Introduction

Cycloplegic central autorefraction is the primary outcome measure of the study. Ten valid measurements are performed on each eye. Dry (non-cycloplegic) autorefraction measurements will also be made at visit 1 (baseline) and every six months thereafter.

Prior to performing autorefraction, the settings of the autorefractor should be checked by pressing the "mode" button. The settings should be as follows:

- STEP 0.12
- VD(mm) 0
- CYL (–)
- START MAN.N
- REF NORMAL
- KERATO DIOPT
- SE OFF
- PRINT FORM ALL
- DATA SCREEN OFF
- W-D (cm) OFF
- SCREEN ADJ Up to each site. Typically set at about 60%.

SECOND SCREEN

- SAVE 10
- PD CENTER OFF
- BUZZER LOW
- OPTION MESSAGE No. RS232C
- DATE FORM MDY

(Press IOL button to access the RS232 screen)

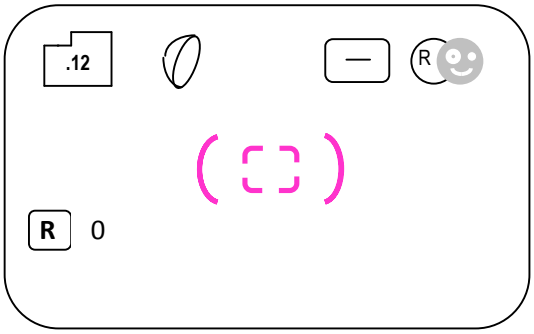
RS232C SCREEN

- BAUDRATE 9600
- CHARACTER 8
- PARITY NONE
- STOP BIT 1

(Press IOL button to exit)

When ready to measure a subject, the screen should be set to measure refraction only (R). When first turned on, the instrument default is to measure refraction (R), pupil diameter (P.Diam), and to say "FAR" on the screen. Press the "ACOM · RK" button until set to only measure refraction (R). The screen will look like Figure 15-1 when set appropriately.

Figure 15-1: Appearance of the autorefractor screen prior to measurement of the subject.



Calibration

Calibrate the Grand Seiko every month or after the autorefractor is moved. Transmit the calibration of the autorefractor to the REDCap on the Calibration Form.

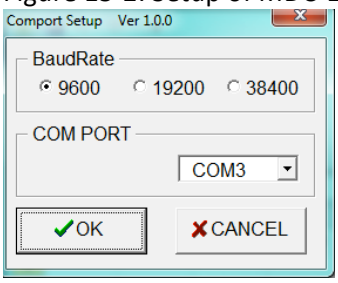
1. Place the model eye on the chin rest and ensure that the base of the model eye is parallel to the chin rest with the face of the model eye perpendicular to the measurement axis of the autorefractor.
2. Allow the autorefractor to warm up for 15 minutes.
3. Center the focused mires in the middle of the pupil of the model eye. Take 10 readings with *complete re-focusing* between each reading.
4. Print the spherocylindrical readings and tape them in the Autorefractor Calibration Form.

Laptop Computer Setup

Electronic data capture of Grand Seiko autorefraction measurements will be accomplished using Microsoft Excel and MDC add-in software. Once the MDC software is initially setup, changes should not be necessary.

1. Launch Microsoft Excel.
2. Click on the “Add-In” tab in the Ribbon at the top of the screen.
3. Click MDC-1 and then select “Setup.”
4. In the Setup window that appears, the BaudRate should be set to 9600, and the COM PORT should be set to COM3 so the setup screen looks like Figure 15-2.

Figure 15-2: Setup of MDC-1 for electronic data capture.



Cycloplegic Drops

Before cycloplegic autorefraction, three topical drops are instilled in each eye to achieve cycloplegia after inspection of the anterior chamber angle of the eye. The following procedure should be followed:

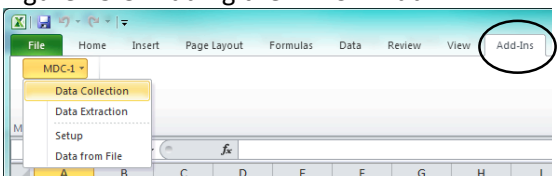
1. Instill one drop of 0.5% proparacaine in each eye.
2. Instill one drop of 1.0% tropicamide in each eye.
3. Wait five minutes.
4. Instill a second drop of 1.0% tropicamide in each eye.
5. Write the time of the second drop of tropicamide on a piece of paper.
6. Wait 25 minutes after the second drop of tropicamide to perform cycloplegic measures.

Measurement Procedure (Dry and Cycloplegic Autorefraction)

The measurement procedure is the same for both cycloplegic autorefraction and for dry autorefraction. All autorefraction measurements will be electronically collected via an attached laptop computer in a Microsoft Excel spreadsheet, which will then be uploaded to the REDCap.

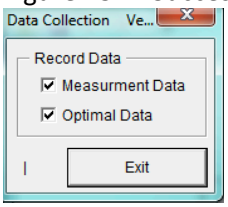
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated COM3).
2. Navigate to the central autorefraction Excel Template file (CentralAuto_Template.xltx) located in the "BLINK Templates" folder on the desktop and open the file.
3. Once Excel opens the template, click the "Add-Ins" tab in the ribbon and click "MDC-1" and select "Data Collection" (Figure 15-3).

Figure 15-3: Adding the MDC-1 Add-In.



4. Once the Grand Seiko successfully connects to the laptop, you will see the following window (Figure 15-4).

Figure 15-4: Successful connection between autorefractor and laptop.



5. Slide the +5.50 D Badal track into place at the central (0°) slot on top of the Grand Seiko.
6. Put a patch over the subject's left eye so that the right eye can be measured.
7. Place the subject's chin on the chinrest. Attach the forehead rest during central autorefraction measurements and make sure the subject's forehead is touching the forehead rest. The forehead rest should be removed for peripheral autorefraction.
8. Place the letter target on the Badal track initially at the 0 diopter mark. Ask subject if the letters are clear. If yes, instruct subject to report when letters become fuzzy. Slide card slowly away from the lens until subject reports blur.
9. If the letters are not clear at 0 diopters, move the target forward (toward the Badal lens), instructing subject to tell you when the letters first become clear. Once the letters first look clear, stop and back the card off slightly (approximately 1 cm). If the letters are still blurred with the target at the closest position, instruct the subject to look at the center of the target and proceed.
10. Locate the subject's eye on the Grand Seiko monitor and center the pink reticule so that the inner portion of the pink reticule is within the white ring and the outer portions of the pink reticule are just outside the white ring as shown below (Figure 15-5).

Figure 15-5: View in autorefractor that shows proper alignment.

11. Move joystick toward or away from the subject to focus the ring. When the white ring is in focus, measurements may be taken.
12. Instruct the subject to pick one letter and stare at it. Take at least 10 “good” readings, meaning the eye is aligned and no “retry” message appears when taking a measurement.
13. Press the “Print” button on the autorefractor.
14. Write the Subject ID on the printout and tape it on the examination form where indicated.
15. Switch the patch to cover the right eye so that the left eye can be measured and complete steps 7 through 14.
16. When finished measuring each eye, click the “Exit” button on the laptop to end the connection between the Grand Seiko and laptop.
17. Save the Excel file under “Documents” in the “BLINK Data” folder using the following file-naming scheme:
    For Cycloplegic Central Refraction:
        SubjectID-CycloAuto-VX (where X is the visit number) – Ex: 204-TJ-CycloAuto-V1.xls
    For Non-Cycloplegic Central Refraction:
        SubjectID-DryAuto-VX (where X is the visit number) – Ex: 204-TJ-DryAuto-V1.xls
18. Upload file to subject’s record using REDCap.

Chapter 16: Accommodative Lag with Manifest Refraction (Baseline Only)

Eyes

OD

Reason for Measuring Accommodative Lag

Accommodative lag has been shown to be related to the myopia control treatment effect with bifocal or multifocal spectacles. It is important that we know the baseline lag characteristics of subjects in BLINK and be able to check whether these baseline lag characteristics are randomly distributed between treatment groups. We will measure the accommodative lag of all subjects using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL).

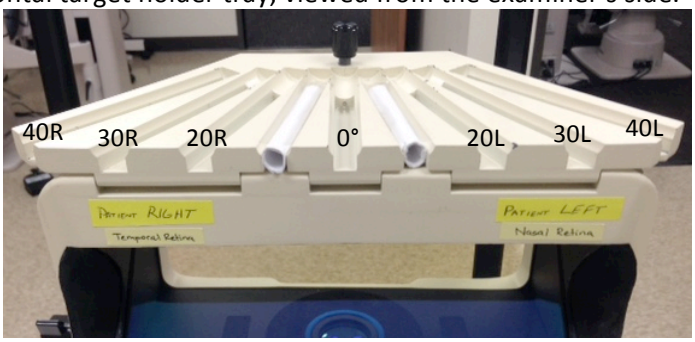
Measurements will be made at 33cm (3-D demand) with the child wearing the manifest refraction in a trial frame. **Accommodative lag with the manifest refraction in a trial frame is measured at Visit 1 (Baseline) only.** The letter target used is 2.06 M in size (20/125 Snellen Equivalent). This letter size is used because it approximates text size in materials read by children in this age group.

All Grand Seiko settings and laptop computer settings are the same as noted in the *Central Autorefraction* chapter. This lag measurement will be included in the Visit 1 dry central autorefraction Excel file that was already created when measuring dry central autorefraction OD and OS earlier in the baseline (Visit 1) examination.

Measurement Procedure

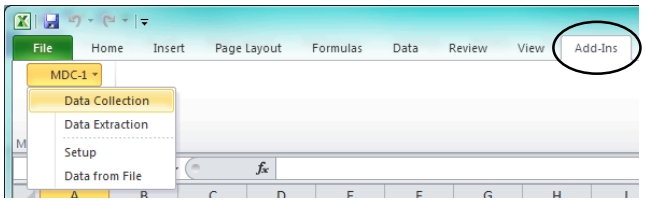
These measurements are performed on the right eye only with normal accommodation (i.e., NO cycloplegia). A picture of the autorefraction horizontal target holder tray (examiner side) is shown in Figure 16-1.

Figure 16-1: autorefraction horizontal target holder tray, viewed from the examiner's side.



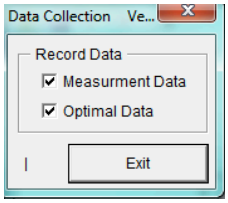
1. The Grand Seiko should still be connected to the laptop from having performed dry central autorefraction OU earlier during Visit 1. Confirm that the computer is still connected to the autorefractor.
2. If necessary, reconnect the MDC-1 software from within the "Add-Ins" tab in the Microsoft Excel ribbon (Figure 16-2) by clicking "MDC-1" and selecting "Data Collection" as described in the *Central Autorefraction* chapter.

Figure 16-2: Click on the Add-Ins tab in Excel.



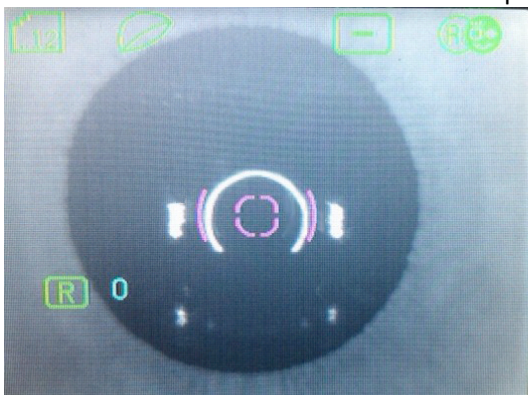
3. When the Grand Seiko is successfully connected to the laptop, you will see the window in Figure 16-3.

Figure 16-3: Signifies successful connection to laptop.



4. Place the manifest correction used for visual acuity on the child in a trial frame. Attempt to minimize the number of lenses used in the trial frame. The Grand Seiko will read accurately through one or two trial lenses, but may not through three.
5. Place an occluding trial lens in the trial frame well over the left eye so that the child will only view targets with the right eye.
6. Place the 33cm near rod in the central slot to measure accommodative lag in primary gaze only.
7. Place the subject's chin on the chinrest. The forehead rest can be attached if needed. Otherwise, it may be necessary to have assistance holding the subject's head in place during measurements.
8. Obtain a view of the eye on the screen. The white keratometry circle should be in focus. The pink reticule is centered within the white keratometry ring as shown in (Figure 16-4).

Figure 16-4: View in autorefractor that shows proper alignment.



9. Encourage the child to keep the letters as clear as possible throughout the measurement and have the child focus on a specific letter to ensure the child is attentive and accommodating.
   (Important: Constantly remind the child to keep the letters clear when taking measurements!)
10. Obtain at least five readings without the "retry" message. When in doubt, take additional measurements to ensure that at least 5 measurements exist.
11. Press Print and tape the printout in the location indicated on the exam form.
12. When finished measuring, click the "Exit" button on the laptop to end the connection between the Grand Seiko and laptop.
13. This file should now contain both the Non-cycloplegic central autorefraction measurements OD and OS followed by the Visit 1 accommodative lag measurement just taken with the manifest refraction (in that order). Save the Excel file in "Documents" in the "BLINK Data" folder using the following file naming format:
    SubjectID-DryAuto-VX (where X is the visit number) – Ex: 204-TJ-DryAuto-V1.xls
14. Upload the data file to subject's record using REDCap.

Chapter 17: Axial and Peripheral Eye Length

Eyes

OD and OS for central eye length and OD only for peripheral eye length

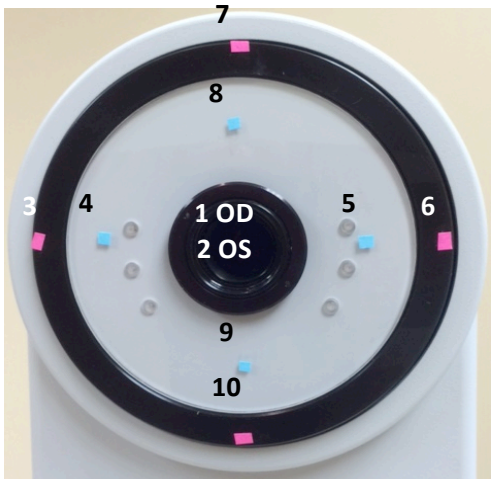
Equipment

Optical low-coherence reflectometry is performed to measure the axial dimensions of the eye with the Lenstar LS 900 (Haag-Streit USA, Mason, OH). One push of the button provides central corneal thickness, anterior chamber depth, lens thickness, vitreous chamber depth, axial length, keratometry, pupillometry, and corneal diameter.

Introduction

Measurement of eye length with the Lenstar LS requires cycloplegia for accurate measurement but no corneal anesthesia. One push of the button while in primary gaze provides central corneal thickness, anterior chamber depth, lens thickness, vitreous chamber depth, axial length, and keratometry. Measurements of eye length only will be recorded in peripheral gazes. Measurements will be recorded while the subject looks in primary gaze on the right eye then the left eye, followed by the subject turning his right eye (left eye patched) to look 30˚ left and 30˚ right – in that order (Figure 17-1). The targets at 30˚ are located 37.5 mm from the center of the aperture.

Figure 17-1: Order of eye length acquisition from the subject's perspective.



Calibration

The Lenstar LS 900 automatically prompts you to calibrate every week.

1. Make sure nothing is in front of the Lenstar measuring apparatus.
2. Press "Next" on the screen to initiate the nullification process.
3. When the "Completed" screen appears with a green smiley face, press "Exit."
4. Mount the model eye just under the forehead rest and push it all the way up on both sides.
5. Press "Next" on the screen.
6. Focus ring of lights on model eye (viewed on screen), with central blinking light in middle of crosshairs.
7. Press the button on the joystick.
8. In the high magnification view on the screen, push slightly in or out according to the arrows on the screen (out if arrow points down or in if arrow points up) until you obtain a *small* green circle in the center of the view.
9. Press the button on the joystick.
10. Click "Exit" on the screen.
11. Write the date of the calibration on the Axial Length Calibration Form and transmit the data to the REDCap.

Procedure

Open the EyeSuite application by double clicking the icon in the middle of the screen. Make sure you are in the correct database. All of the subjects should start with BLINK. If not, go to Tools → Preferences →General →Database. In the Database: box, enter 'blink' for the BLINK Study database or 'octosoft' for the default database. Click OK, then restart EyeSuite.

1. Press the **Patients** icon on the left side of the screen.

2a. For a new subject, click "new" on the right side of the screen. Enter BLINK in the **Name** box so that all BLINK subjects are grouped together. Enter Subject ID-Number-Measurement in the **First Name** box. The Subject ID should include the initials; the number is a designation to maintain the order of the files on the screen in the same order as they are performed; and the measurement performed (L=left gaze, R=right gaze, U=up gaze, D=down gaze, 30=30 degrees, and 20=20 degrees). In **Date of Birth,** enter "01/01" and the subject's year of birth. **Gender** is not necessary and should not be entered. A different file is created for each location. Each of the files can be created prior to the appointment, then deleted if the patient is ineligible. To delete unnecessary files, simply highlight the files on the **Patient** screen, then press **Delete** on the keyboard. Press **Save** in the bottom right when done.

Example of the file names you would create for subject 024:

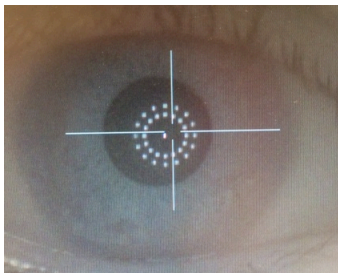
Name	**First Name**	**Date of Birth**
BLINK	024-JT-1-C	1/1/2004
BLINK	024-JT-2-30L	1/1/2004
BLINK	024-JT-5-30R	1/1/2004

Note: The measurement designated above is the direction the patient should look (L means the patient should look to his left). You measure nasal retina when the patient looks left, temporal retina when the patient looks right, superior retina when the patient looks up, and inferior retina when the patient looks down.

2b. For a returning subject, type BLINK in the top left box, then scroll down and click on the appropriate file in the list below.

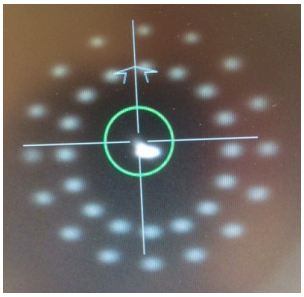
3. Press the Biometry icon on the left side of the screen.
4. Patch the left eye and have the subject put the chin in the chin rest and forehead against the bar with head straight.
5. Press the button on the joystick.
6. Focus the ring of lights viewed on screen, with central blinking light in middle of crosshairs (Figure 17-2).

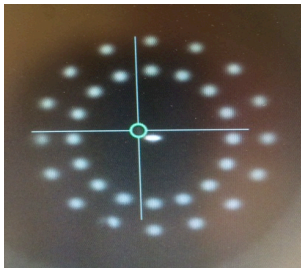
Figure 17-2: The unmagnified view of the eye. Focus the circles of dots, and place the blinking light in the crosshairs.



7. Press the button on the joystick to obtain a more magnified view.
8. Push the instrument slightly in (arrow pointing up) or out (arrow pointing down) until you obtain *small* green circle in center of view (Figure 17-3).

Figure 17-3: The arrow pointing up indicates the joystick should be pushed toward the patient in the top picture, and the small green circle in the lower picture indicates good focus.





9. Press the button on the joystick.
10. A white circle will begin to form. You may need to focus slightly to get the white circle to complete. The measurement is finished when the white circle completes.
11. Tell the subject to blink, and press the button on the joystick.
12. Repeat steps 3 through 10, obtaining five measurements at each position. *In central gaze*, no measurements should have a ⚠ icon next to it. If a measurement has this icon, delete it by clicking on it and pressing **Delete** on the keyboard. If you have replaced three measurements, then you can stop replacing them, as long as you have five measurements. In peripheral gaze, nearly every measurement will have a ⚠ icon, so simply collect five readings.
13. Print results after each measurement by double clicking Lenstar icon under Examinations and hitting **Control-P.** Place the printouts in the Baseline Examination or Annual Examination Form.
14. Click Finish, then go back to Patients to select the next gaze direction.
15. Exit the EyeSuite application when done with measurements. Say **No** to Database Backup (it will take about 30 minutes). Shut down the computer using the Microsoft logo in the bottom left corner of the screen.

Data Download

Data should be downloaded from Lenstar weekly. We cannot choose the data to be downloaded so all data stored on the Lenstar must be downloaded each time. A template with the name CSV_BLINK is provided to guide the export.

1. Place a USB drive in the USB port on the hard drive of the Lenstar.
2. Open EyeSuite.
3. Click on **Tools**, then **Reporter**.
4. In the **Template File:** box, enter C:\Users\LenStar\Documents\Templates\CSV_BLINK.txt
5. Click **Next**
6. In the **Report File**: box, enter C:\Users\LenStar\Documents\BLINKOutput\clinic.MMDDYY.csv (date is date of download)
   - Example: C:\Users\LenStar\Documents\BLINKOutput\OSU.041714.csv
   - Example: C:\Users\LenStar\Documents\BLINKOutput\UH.110914.csv
7. Click Next. The Lenstar will give you a prompt that the report was generated successfully.
8. Click Exit
9. In REDCap under Applications, select File Repository.

10. Choose upload new file. Select the file, and upload into the repository. The OCC will download from the File Repository once a week, and remove it from the repository so the data do not remain accessible.

Chapter 18: Peripheral Refractive Error Without Contact Lens

Eyes

OD

Equipment

Peripheral refractive error will be measured using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL).

Reason for Measuring

Peripheral refractive error without a contact lens is a surrogate for shape of the eye. Most longitudinal myopia studies have used peripheral refractive error as a measure of eye shape. Peripheral refractive error will be measured using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer along the horizontal and vertical meridian of the eye. All Grand Seiko settings and laptop computer settings are the same as noted in the *Central Autorefraction* chapter.

The Grand Seiko has been modified to allow for either a laser pointer (distance measurements) or a near point rod (near measurements) to be placed centrally or out to 40° from the line of sight in 10° increments along the horizontal meridian. Measurements in the horizontal meridian will be made at ±30° from the line of sight. (Note: No measurements will be made at ±10°, ±20° and ±40°, and these slots should be filled to prevent accidental placement of a target in these locations).

Autorefractor Setup

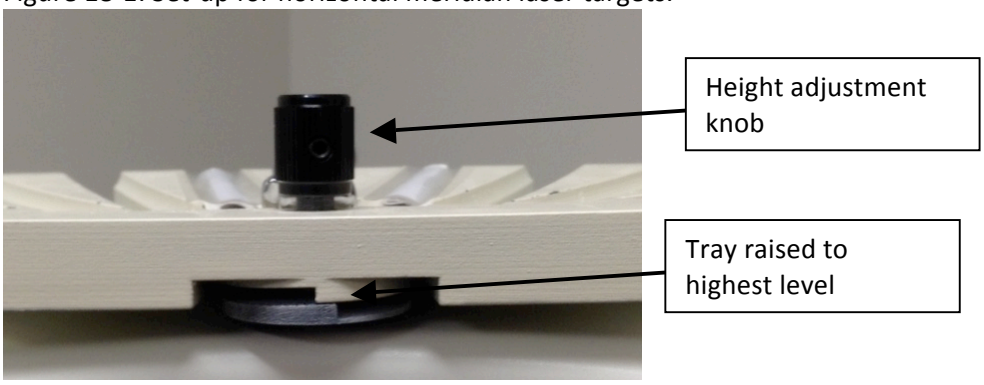
Distance from wall

The autorefractor should be fixed in location such that the entrance pupil of the eye is located 1.5 meters (4.9 ft) from the wall for all measurements.

Target Holder Setup

For the horizontal meridian laser targets to be at eye level for distance measurements when the entrance pupil is 1.5 meters from the wall, the height adjustment knob on the subject side of target holder tray must be rotated so that the back of the tray is at its highest level (Figure 18-1).

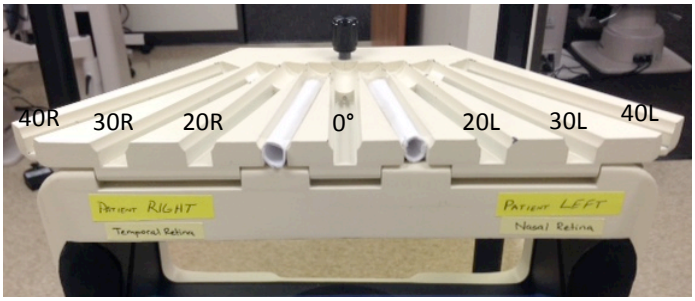
Figure 18-1: Set-up for horizontal meridian laser targets.



Measurement Procedure (Horizontal Meridian)

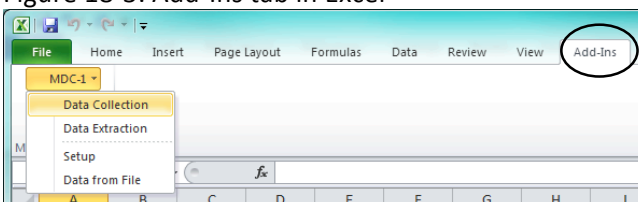
These measurements are performed on the right eye only under cycloplegia. Left and right refer to the direction the subject looks. A picture of the autorefraction horizontal target holder tray, seen from the examiner's side (Figure 18-2).

Figure 18-2: Autorefraction horizontal target holder tray.



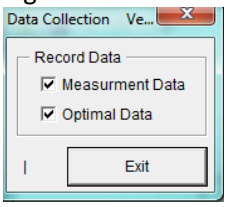
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated as COM3).
2. Navigate to the peripheral autorefraction Excel Template file (PeripheralAuto_Template.xltx) located in the "BLINK Templates" folder on the desktop and open the file.
3. Once Excel opens the template, click the "Add-Ins" tab (Figure 18-3) in the ribbon and click "MDC-1" and select "Data Collection".

Figure 18-3: Add-Ins tab in Excel



4. Once the Grand Seiko successfully connects to the laptop, you will see the following window (Figure 18-4).

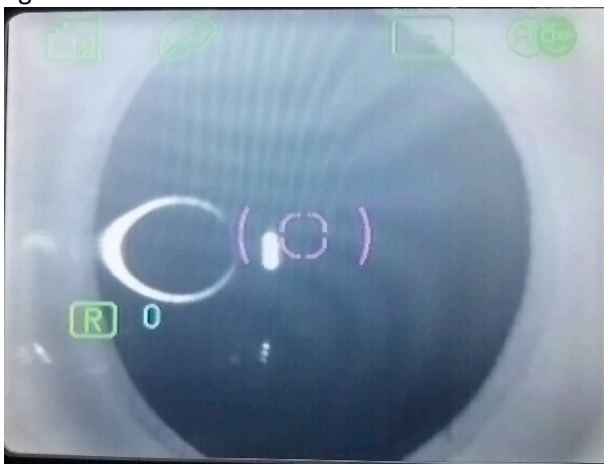
Figure 18-4: Window signifying successful connection to laptop.



5. Place an eye patch over the subject's left eye.
6. Place the subject's chin on the chinrest. The forehead rest is not used for horizontal measurements because it prevents accurate instrument focusing during measurements. It may be necessary to have assistance holding the subject's head in place during measurements.
7. Turn on the laser pointer and place it in the appropriate slot to measure with the subject looking 30° to his/her Left (temporal retina).
8. Tell subject to keep looking straight ahead with eyes, but to turn head (guide with your hands) so that they are looking straight at the laser spot on the wall. Visually inspect to ensure that the subject's eyes are in primary gaze and the subject's head/nose is pointed directly at the laser spot on the wall.
9. Obtain a view of the eye on the screen. For peripheral measurements, find the best iris focus by moving the instrument in or out. *Note: For peripheral measurements, the iris is used to focus (not the white keratometry circle).*
    - Exception: For central measurements *ONLY* (0°), the white keratometry circle should be in focus as shown in the *Central Autorefraction* chapter.
10. Center the pink reticule in the horizontal meridian and vertical meridian of the pupil. *Note: For peripheral measurements, do not center the pink reticule in the center of the white keratometry circle reflecting off the cornea!* An example showing correct horizontal centration for a *peripheral measurement* is shown below (Figure 18-5).

- Exception: For central measurements *ONLY* (0°), the pink reticule is centered within the white keratometry ring as shown in the *Central Autorefraction* chapter.

Figure 18-5: Pink reticule centered in the horizontal and vertical meridians of the pupil.



11. Obtain at least five "good" readings in which neither the sphere nor cylinder differ from the median by more than 1.00 D. When in doubt, take additional measurements to ensure that at least 5 "good" measurements exist.
12. Press Print and tape the printout in the location indicated on the exam form.
    (Important: Remember to press the print button between each change in gaze!)
13. Repeat steps 8 through 12 with the laser pointer at Central (0°) and 30° Right (30R).
    (Note: It is important that you always follow this order – 30L, Central, 30R. If you ever accidentally go in a different order, this must be noted in the Excel file once measurements are complete.)
14. When finished measuring the horizontal meridian, click the "Exit" button on the laptop to end the connection between the Grand Seiko and laptop.
15. Save the Excel file in "Documents" in the "BLINK Data" folder using the following file-naming scheme: SubjectID-NoLens-Horiz-VX (where X is the visit number) – Ex: 204-TJ-NoLens-Horiz-V1.xls
16. Upload the horizontal data file to subject's record using REDCap.

Chapter 19: Peripheral Defocus With Contact Lens at Distance

Eyes

OD

Equipment

Peripheral refractive error will be measured using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL).

Reason for Measuring Peripheral Defocus With Contact Lens

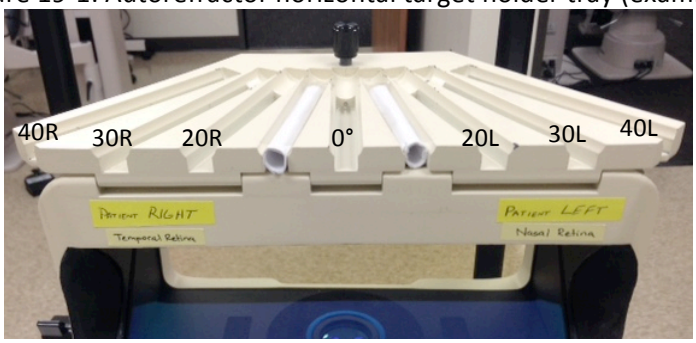
Peripheral defocus with the subject wearing their study contact lens measures the optical defocus that the peripheral retina receives while wearing the contact lens. Measurements are made at Visit 1 (Baseline) and at Visits 5, 7, and 9. All Grand Seiko settings and laptop computer settings are the same as noted in the Central Autorefraction chapter.

The Grand Seiko has been modified to allow for either a laser pointer or a near point rod to be placed out to 40° from the line of sight in 10° increments along the horizontal meridian. Measurements in the horizontal meridian will be made centrally (0°) and at ±30° from the line of sight. No measurements will be made at ±10°, ±20°, and ±40°, and these slots should be filled to prevent accidentally placing a target in these locations.

Measurement Procedure (Horizontal Meridian)

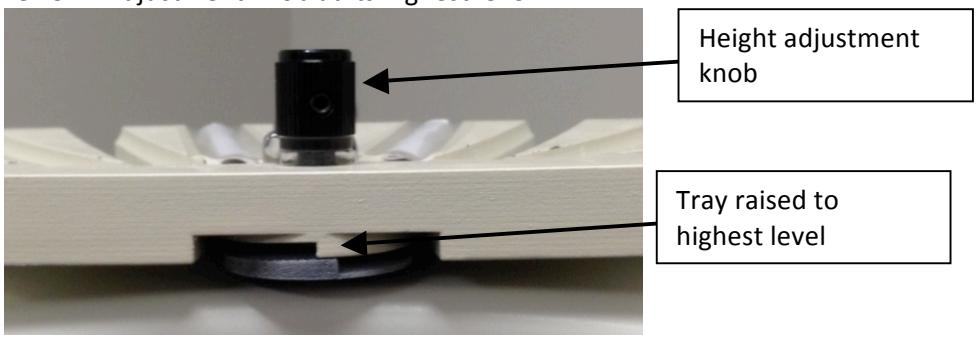
Left and right refer to the direction the subject looks. Figure 19-1 shows the autorefractor horizontal target holder tray (examiner side).

Figure 19-1: Autorefractor horizontal target holder tray (examiner side).



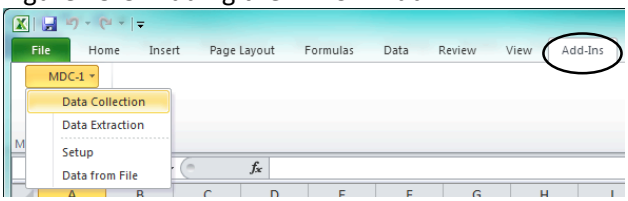
Before beginning, verify that the height adjustment knob on the subject side of target holder tray is rotated so that the back of the tray is at its highest level (Figure 19-2).

Figure 19-2: Adjustment knob at its highest level.



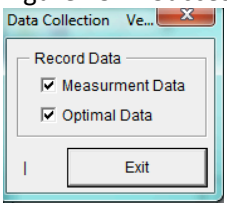
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated as COM3).
2. Navigate to the peripheral autorefraction Excel Template file (PeripheralAuto_Template.xltx) located in the "BLINK Templates" folder on the desktop and open the file.
3. Once Excel opens the template, click the "Add-Ins" tab in the ribbon and click "MDC-1" and select "Data Collection" (Figure 19-3).

Figure 19-3: Adding the MDC-1 Add-In.



4. Once the Grand Seiko successfully connects to the laptop, you will see Figure 19-4.

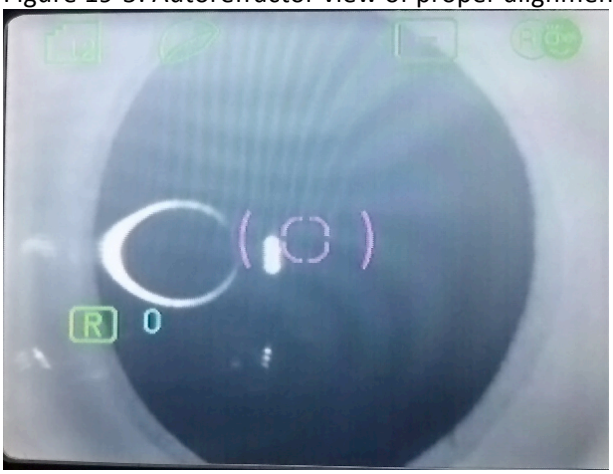
Figure 19-4: Successful connection between autorefractor and laptop.



5. Place an eye patch over the subject's left eye.
6. Place the subject's chin on the chinrest. The forehead rest is not used for horizontal measurements because it prevents accurate instrument focusing during measurements. It may be necessary to have assistance holding the subject's head in place during measurements.
7. Turn on the laser pointer and place it in the appropriate slot to measure with the subject looking 30° to his/her Left (nasal retina).
8. Tell subject to keep looking straight ahead with eyes, but to turn head (guide with your hands) so that they are looking straight at the laser spot on the wall. Visually inspect to ensure that the subject's eyes are in primary gaze and the subject's head/nose is pointed directly at the laser spot on the wall.
9. Obtain a view of the eye on the screen. For peripheral measurements, find the best iris focus by moving the instrument in or out. *Note: For peripheral measurements, the iris is used to focus (not the white keratometry circle).*
   Exception: For central measurements *ONLY* (0°), the white keratometry circle should be in focus as shown in the *Central Autorefraction* chapter.

10. Center the pink reticule in the horizontal meridian and vertical meridian of the pupil. *Note: For peripheral measurements, do not center the pink reticule in the center of the white keratometry circle reflecting off the cornea!* An example showing correct horizontal centration for a *peripheral measurement* is shown below (Figure 19-5).
    Exception: For central measurements *ONLY* (0°), the pink reticule is centered within the white keratometry ring as shown in the *Central Autorefraction* chapter.

Figure 19-5: Autorefractor view of proper alignment when performing peripheral refraction.



11. Obtain at least five "good" readings in which neither the sphere nor cylinder differ from the median by more than 1.00 D. When in doubt, take additional measurements to ensure that at least 5 "good" measurements exist.
12. Press Print and tape the printout in the location indicated on the exam form.
    (Important: Remember to press the print button between each change in gaze!)
13. Repeat steps 8 through 12 with the laser located at Central (0°) and 30° Right (30R).

(Note: It is important that you always follow this order – 30L, Central, 30R. If you ever accidentally go in a different order, this must be noted in the Excel file once measurements are complete.)

14. When finished measuring the horizontal meridian, click the "Exit" button on the laptop to end the connection between the Grand Seiko and laptop.
15. Save the Excel file in "Documents" in the "BLINK Data" folder using the following file-naming scheme:
    SubjectID-CLDist-Horiz-VX (where X is the visit number) – Ex: 204-TJ-CLDist-Horiz-V1.xls
16. Upload the horizontal data file to subject's record using REDCap.

Chapter 20: Videophakometry

Eyes

OD

Equipment

Videophakometer

Reason for Measuring

Videophakometry measures lens curvature. Measurement of lens radii of curvature is analogous to measurement of corneal curvature. The size of a reflected image is proportional to the radius of curvature of the reflecting surface. Comparison of the separations of pairs of Purkinje images I (cornea), III (anterior lens surface), and IV (posterior lens surface) to values from calibration on steel balls of known radius yields radii of curvature in air for each of these surfaces. Later calculations transform these raw values in air to radii of curvature in the eye. Additionally, the calculations yield an individual equivalent index of refraction for the crystalline lens.

Equipment Setup

Cables should be arranged in the following manner:

(1) A video cable should go from the VID 1 output port on the camera control box to the Video In port on the VCR 1 output port on the camera control box to the Video In port on the VCR.
(2) A video cable should go from the Video Out port on the VCR to the Video In port on the TV Monitor, with the monitor set to Line Input.
(3) The camera control cable should go between the camera and the camera control box.

The Light source should be to the left of the slit lamp base with the lights arranged vertically.

The camera control box should be set to the following:

- Enhance – Minimum
- Bandwidth – Maximum
- Gamma – 9.45
- Stretch – On
- Polarity – Positive
- Black Level – Preset and Auto (both toggle switches down)
- Gain – Auto (toggle switch down)
- Gain Switch at back of control box – LO (down)
- Camera Aperture – F2.8

Calibration

The phakometer is calibrated by finding the size of reflections from steel ball bearings of radii 11.91, 9.53, 8.735, 8.345, 7.94, 7.55, 7.135, 6.35, and 5.955 mm. The balls are held in place by a magnetic attachment to the chinrest of the phakometer. Calibration should be performed each time the phakometer is moved between schools.

(1) Change the aperture of F4. Remember to change back to F2.8 at the end of calibration. The aperture is changed because of the high reflectivity of steel.
(2) Record a tag for the calibration with school or location, date, and the radius of the ball.
(3) Place the largest ball (longest radius) into the magnetic holder (it may need to be held in place by hand).
(4) Turn the light source to the lowest setting. Obtain best focus for the two light sources and record for 5 seconds.
(5) Move the slit-lamp base to blur the images, re-focus and record again for 5 seconds.

(6) Move the slit-lamp base to blur the images one more time- re-focus for a third time and record again for 5 seconds.
(7) Stop the VCR and repeat this process for each successively steeper steel calibration ball. Remember to record the radius for each ball before recording the images.
(8) Procedures for digitization and measurement are described in the following section. Two measurements are taken for each 5 second recording period (total six readings per ball). Copy and paste the average for each ball radius and the ball radius itself into a statistical/graphing program such as Cricket. Perform a linear regression with the radii of the balls as the dependent variable and the average number of pixels per ball as the independent variable. Record the slope and intercept for each calibration occasion, as well as which patients are measured at that site.

Measurement

(1) Write the ID#s of the subjects to be measured on a chronological log sheet. Record the ID#s of the subject to be tested on the videotape prior to measurement. Retain the log sheet for later use by the reading center.
(2) Position the patient either sitting or standing comfortably at the chinrest. Turn on the fixation light and the fiber optic light source. Adjust the height of the chinrest, not the slit lamp, in order to bring the reflected images to the middle of the monitor screen. This keeps the light sources and the camera at the same level.
(3) With the illumination of the light sources low, move the fixation light so that it appears between the two Purkinje I images. Find the best focus of Purkinje image I. They should be small, nearly round, and equal in size. Avoid clipping of the images by the eyelids. Record for about 10 seconds.
(4) Turn up the intensity of the light sources. Purkinje image IV is in nearly the same focal plane as Purkinje image I and should come into view. Adjust the fixation light to bring the midpoint of the two Purkinje image IVs to the same level as the Purkinje image Is. They should be placed to the right of the Purkinje image Is on the monitor screen in order to keep them distinct. Purkinje image IV will move in the same direction as the fixation light. Often the fixation light obscures Purkinje image IV and must be switched off and on during measurement. Find the best focus for Purkinje image IV and record for about 6 seconds or switch the light off and on six times.
(5) Move the slit-lamp toward the patient by about 1 cm to find the focal plane for Purkinje image III. Adjust the fixation light to bring the midpoint of the two Purkinje image IIIs to the same level as the Purkinje image Is. Adjust the intensity of the illumination to produce visible Purkinje image IIIs. They should be placed to the right of the Purkinje image Is on the monitor screen in order to keep them distinct. Purkinje image III will move in the opposite direction of the fixation light. If the fixation light obscures Purkinje image III, it must be switched on and off during measurement. Find the best focus for Purkinje image III and record for about 3 seconds or switch the light off and on once.
(6) Stop the VCR and turn off the illumination.

Chapter 21: Survey Administration

Surveys

The Contact Information and History Forms contain personal identifying information, so they should not be sent to the REDCap. All other forms will be completed online by the appropriate person, at the Visits indicated in Table 21-1.

Table 21-1: Forms, when completed, by whom, and whether or not they are sent to the Data Coordinating Center.

Forms	Completed by	Not sent to REDCap	Visit 1	Visit 2	Visit 3	Visits 4, 6, 8	Visits 5, 7, 9
Contact Information	Parent/Guardian	X	X			Update	Update
History	Parent/Guardian	X	X				Update
Myopia Risk Factor	Parent/Guardian		X				
Contact Lens	Subject				X	X	X
Atropine Side Effects	Parent/Guardian		X		X	X	X
CISS	Subject		X		X	Visit 4 only	X
Parent Compliance forms (Atropine & CLs)	Parent/Guardian				X	X	X

Guidelines

The following are guidelines for survey administration.

1. Ask the appropriate person to complete a survey during a time that the computer is not needed for data entry and the person is free to answer questions.
2. All surveys should be read and answered by the appropriate person only. Ask parents not to help their child answer questions.
3. If the child has difficulty completing the survey, the examiner may read the survey to the subject. The subject's parent may not read the survey to the child.
4. The examiner may answer questions about the meaning of a word, but must be careful not to guide the subject to make a specific answer. The subject must freely choose his or her own answer.

Chapter 22: Contact Lens Insertion, Removal, and Care Instructions

Eyes
OU

Procedure
1. Tell the subjects to always wash hands before handling contact lenses
2. Seat the subject in front of mirror with solutions and case nearby
3. If the subject is right handed, tell her to gently pull the center of the top eye lid to the brow with the left hand
4. With the middle finger of the right hand, pull the central edge of the lower eyelid to the cheek bone
5. While looking in the mirror, place the soft part of the thumb and finger on either side of the colored part of the eye, pull the lens onto the white part of the eye, and pinch to the middle
6. When the contact lens begins to fold, pull the contact lens off of the eye
7. Show the subject how to clean the contact lens
    a. Place the contact lens on the palm of the hand
    b. Pour a little solution on the contact lens
    c. Rub the contact lens side-to-side in a straight line for five seconds, then up-and-down for five seconds
    d. Flip contact lens inside out
    e. Rub the contact lens side-to-side in a straight line for five seconds, then up-and-down for five seconds
    f. Turn the contact lens right-side-out, place in case, and cover with solution
8. Repeat steps 1 through 7f, but have the subject clean the contact lens this time.
9. Place the contact lens on the right index finger (if right handed)
10. Gently pull the center of the top eye lid to the brow with the left hand
11. With the middle finger of the right hand, pull the central edge of the lower eyelid to the cheek bone
12. While looking in the mirror, touch the contact lens to the cornea
13. When the contact lens is on the eye, pull the right index finger away from the lens, but don't let go of the top eyelid
14. Either look all around or rub the lower eyelid until the contact lens settles on the eye
15. Let go of the top eye lid
16. Repeat steps 9 through 15 for the left eye, using the same hands for the above tasks
17. Discard all solutions from the case
18. Rub the inside of the case with a tissue or paper towel
19. Store the case and lids upside-down on a tissue or paper towel all day
20. Tell the subject about proper care of the contact lenses
    a. Never sleep with contact lenses in your eyes
    b. Replace your contact lenses every month
    c. Use a new case every time you open a new bottle of solution
    d. Never use tap water on your contact lenses; only the solutions we provide
    e. Swim with goggles or remove the contact lenses right after swimming and store them in solution overnight.
    f. Remove the contact lenses if the eyes are red, painful, or can't see; if they improve wear contact lenses the next day; if they don't improve call the study emergency number

The subject must remove and insert the contact lens from each eye before taking contact lenses home.

Chapter 23: Glasses and Contact Lenses

Glasses

All subjects are eligible to receive a free pair of spectacle frames and lenses one time per year. Subjects will receive a prescription for glasses at study closeout, and a new pair of spectacles. If subjects lose or break their spectacle frames, new ones will be provided by the study if they are not still under warranty. In addition, new spectacle lenses may be provided if a spectacle prescription is found to have changed ≥–0.50 D or if it is deemed to be clinically necessary to improve vision.

Each clinic will provide free polycarbonate, single vision lenses. All frames less than $150 retail are provided at no charge. If a frame worth more than $150 retail is chosen, the subject pays the difference. For example, if a subject picks out a frame that retails for $200, then the subject pays $50 for the pair of glasses. If a subject desires transitions lenses, clip-on sunglasses, tinted lenses, or any other item that costs extra, the subject may pay retail cost for the extra item(s) and add them to their glasses.

Contact Lenses

All subjects will receive free contact lenses throughout the entire study. The contact lenses will be provided at no charge. All subjects will be fitted with Biofinity or Biofinity Multifocal "D" contact lenses. If an appropriate fit cannot be achieved with Biofinity or Biofinity Multifocal "D" contact lenses, subjects will be fitted with Proclear or Proclear Multifocal "D" contact lenses. The subjects will also receive free contact lens cases every three months and contact lens solutions as necessary. If a subject requires a prescription change between six-month visits, new contact lenses will be provided for the subject. If a subject becomes allergic to the solution provided, an alternate solution should be provided for the subject. A new contact lens power may be provided if the over-refraction exhibits a change of ≥–0.50 D, or if it is deemed to be clinically necessary to improve vision. Subjects should be encouraged to wear their contact lenses during all waking hours, but they should also be reminded that they can wear their glasses any time they wish.

Contact Lens Options

All subjects will be fitted with one of the contact lenses in Table 23-1. The first lens fit is the Biofinity or Biofinity Multifocal "D". Proclear contact lenses are only fitted in the event that Biofinity contact lenses do not fit adequately.

Table 23-1: Lenses to be fit during the study.

	Primary		Backup	
	Biofinity	Biofinity Multifocal "D"	Proclear	Proclear Multifocal "D"
Material	Comfilcon A	Comfilcon A	Omafilcon A	Omafilcon A
Water Content	48%	48%	60%	60%
Base Curve	8.6	8.6	8.2, 8.6	8.7
Diameter	14.0	14.0	14.2	14.4
Add Power	None	+1.50 D or +2.50 D	None	+1.50 D or +2.50 D
Powers	up to –12.00 (–0.50 steps > –6.00)	up to –8.00 (–0.50 steps > –6.00)	up to –20.00 in 8.6 up to –10.00 in 8.2 (–0.50 steps > –6.00)	up to –8.00 (–0.50 steps > –6.50)
dK	128.0	128.0	34.0	34.0
Add power	–	+2.50 D	–	+2.50 D
Dispose	Monthly	Monthly	Monthly	Monthly

The fit should be assessed by the examiner, and decisions about the fit should be made based upon the clinician's knowledge and experience. If deemed clinically necessary, other lenses may be used.

Contact Lens Solutions

All subjects will receive free contact lens solutions throughout the entire study. The subjects will receive contact lens solutions at every six-month visit, and they may request more solution between visits if they run out.

Should a subject become allergic to the contact lens solution, the clinic site may change the subjects' contact lens solution to another brand of multipurpose solution. The clinic site must provide the solution for the subject at no cost to the subject.

Chapter 24: Atropine Sulfate Ophthalmic Solution (0.01%)

The source used in formulating the 0.01% atropine solution will be atropine 1% ophthalmic solution manufactured by Bausch & Lomb. The 1% atropine solution will be diluted to a final concentration of 0.01%. This compounding will be performed at Central Ohio Compounding Pharmacy located at 262 Neil Ave. Suite 130, Columbus, OH 43215, under the direct supervision of a licensed pharmacist. The atropine solution will be provided to the participants free of charge.

For participants who meet the recruitment eligibility criteria except "compliance with atropine" at the baseline visit, we will schedule a 1-week follow-up visit for atropine dispensing as well as contact lens insertion, removal, and care training. At the 1-week Visit, we will prescribe a 2-week supply of 0.01% atropine and give instructions on how to use the eye drops and the side effects of atropine. The participants will be asked to use atropine for 2 weeks (**run-in period**) and then return to clinic to determine final eligibility. We will weigh the atropine with its bottle before giving it to the participant, and ask the participants to bring the remaining atropine to the clinic at the 3-week Visit. We will weigh the remaining atropine with its bottle, and subjects who finish at least 71% of the atropine eye drops based on the weight during the run-in period (missing drops no more than 2 days per week on average) will be eventually enrolled in the study.

The parent / guardian will put one drop of 0.01% atropine in each eye of the child every night before bed, after removing the contact lenses. We ask the parent / guardian to bring the bottles to the clinic at every visit. At each visit after the enrollment (Visit 3), subjects who finish at least 70% of the atropine eye drops based on the weight will be defined as "adequate compliance with atropine" (missing drops no more than 2 days per week on average); otherwise will be defined as "inadequate compliance with atropine".

Although it has been shown that atropine eye drop has minimal side effects at the 0.01% low concentration (Chua, Balakrishnan et al. 2006; Chia, Chua et al. 2012), ocular and systemic side effects of atropine, including pupil dilation, blurred vision at distance and near, dry mouth, fever, and mental confusion will be closely monitored by surveys and objective measurements. The participants will be educated on the side effects of atropine, and be advised to stop the medication should any atropine-related adverse effects occur. The PI's cell phone number will be provided.

Chapter 25: Electronic Data Capture

A database will be designed in Research Electronic Data Capture (REDCap) to be used for data entry during the examination. It will also include the questionnaires that the parents and children will complete on-line. The PI can track the quality of the data, recruitment, and retention of the study, and export data to complete statistical analysis for presentations, papers, and reports.

Forms

All forms for the study will be provided in the Electronic Data Capture (EDC) system, except forms that are to be maintained solely at the clinic site for subject privacy reasons. After each electronic form is completed, it will be printed and placed in the subject's binder (Table 25-1).

Table 25-1 Forms used at each visit during the study.

Forms	Completed by	Visit 1	Visit 2	Visit 3	Visits 4, 6, 8	Visits 5, 7, 9
Contact Information – paper ***Do not send!***	Parent/Guardian	X			Update	Update
History – paper ***Do not send!***	Parent/Guardian	X				Update
Myopia Risk Factor	Parent/Guardian	X				
Baseline Examination	Examiner	X				
One Week Examination	Examiner		X			
Three Week Examination	Examiner			X		
Semiannual Examination	Examiner				X	
Annual Examination	Examiner					X
Contact Lens	Subject			X	X	X
CISS	Subject	X		X	Visit 4 only	X
Parent Compliance (atropine & contact lenses)	Parent/Guardian			X	X	X
Atropine Side Effects	Parent/Guardian	X		X	X	X
Unscheduled Visit – as needed	Examiner					
Discontinuation – as needed	Examiner					
Adverse Event – as needed	Examiner					
Calibration – monthly	Examiner					

Forms Not Transmitted to EDC System

The Contact Information Form, the History Form, and the Randomization Form should never be transmitted to the EDC system to protect the subjects' privacy. These forms should be maintained at the clinic site. The History Form and Contact Information Form should be maintained in the subjects' data chart.

The History Form should be updated at each annual visit. The parent should cross out anything that no longer pertains (e.g., discontinued medications) and add new information as necessary. After the parent reviews the sheet and makes necessary changes, the date should be written in the top remaining set of boxes under the Updated section.

The Contact Information Form should be updated every six months. Information that no longer pertains should be crossed out, and new information should be written in its place. If a new Contact Information Form is necessary, staple the new one to the front of the old one. The purpose of the Contact Information Form is to help the clinic contact the family in case they move. Nobody outside of the clinic will have access to the information, unless the PI needs to search for the subject.

Corrections

Primary data entry is done via the electronic data capture system with paper copies made to facilitate patient care. If a mistake happens or an edit occurs that is fixed in the database, a notation should also be written on any paper study form; the mistake should be crossed out with a single line, and the person correcting the mistake should initial and date

the correction. Mistakes should never be corrected with "white-out." If there is a question about what to record on a form, the question should never be left blank. A note should be written on the form, stating the problem and the best answer or answers.

Data Entry

Computers will be purchased specifically dedicated to data collection during the study. Data will be entered into REDCap in real time as the examination is completed (direct entry of data). Entry will be completed on a wireless-enabled laptop via the secured web interface which operates in any browser format. In REDCap there are modules that allow for the identification of missing data, as well as quality assurance mechanisms. For instance, there will be range checks enabled which will bring up a query when a value outside of a pre-programmed range is entered. In order to keep this value, a justification must be entered for adjudication by the REDCap. Default entries will not be programmed, for example, data will not automatically be completed when a field is bypassed to minimize the likelihood of incorrect data.

Each form has an associated module where the examiner will go to enter the data for that form. Upon completion of that set of measurements, the data are saved to the server at the CCTS. To simplify transmission of survey data from the clinic site to the EDC, REDCap has a new survey module that will be used to allow subjects and parents to complete the surveys during the time of the visit. A link is provided to the subject/parent that takes them to the survey module to complete the required survey. The surveys that are completed by the subject or the parent, as listed in Table 25-1 include the Myopia Risk Factor Survey, the Contact Lens Form, the Convergence Insufficiency Symptom Survey, Atropine Side Effects Survey, and the Parent Compliance Survey.

Several modules are collected from instruments (Grand Seiko and Lenstar). To minimize the amount of data entry required, data from these instruments will be exported as Excel files by the conventions discussed in the associated MOP chapters. Data from the instruments should be transmitted through the upload feature in REDCap within 24 hours of completion of the exam.

Audit Trails

One of the features of the REDCap system is the ability to maintain audit trails. This tracks each form from the time it is entered, recording who entered the data and when it was entered. From that point on, any time a change is made, the person who made, the date it was made, the reason it was changed, and what it was replaced with is recorded. Original data are always retained. Included in these audit trails is the ability to insert comments along with the changes made, to help provide additional information that will help tracking.

Edit Reports

If the EDC system receives study forms with information that is missing or with data that are not reasonable, an Edit Report will be created and sent to the clinic site. If the form is completed by the examiner, every attempt should be made to determine the problem, and the problem should be corrected or an explanation should be provided. If the form is completed by a subject or parent, three phone calls should be made to try to correct the problem. If the problem is not corrected after three phone calls, two letters should be mailed to the subject or parent. The Edit Report must be returned to the PI within one month.

Security

Only authorized users will have access to the system. Each user will be assigned his/her own access identification, which is not to be used to allow others to gain access. Users should log in at the beginning of a session and must log off when finished. If the data system is idle, the user will automatically be logged-off. The amount of time at which log out will occur is modifiable. The system can also be set to lock out access to the system after a pre-determined number of failed log-on attempts. Users will be required to change their password every 90 days, in compliance with the current policies at The Ohio State University.

REDCap exports research data to a SQLserver 2008 project dedicated database on two different servers depending on the presence of PHI. Both of these servers are housed off-site. As such, neither have incoming or outgoing

connections through the Medical Center firewall. Consequently, data from this database cannot be accessed directly by users, authorized or not, from beyond the firewall. The server upon which the BLINK database will reside is the PHI server, requiring an additional level of security. Database accounts for this database will include the principal investigator and his/her designated staff. The CCTS maintains a web application that can be accessed from any workstation on the medical center network. This web application gives the research team access to data for read and write activities. Any PHI collected is stored in a locked down table. Limited access to this table will be granted at the request of the principal investigator. The provisioning of accounts and user access to specific database(s) is integrated with the OSU Medical Center LDAP authentication service for studies containing protected health information (PHI), and the provisioning of access and specific user rights for all studies are managed by CCTS staff. Back-ups are done on both the database and the server on a nightly basis to prevent catastrophic data loss.

Personnel at The Ohio State University will be assigned an OSU Medical Center access identification because of the use of the PHI server. Different levels of user access are determined based upon the role of the user in the study. Similarly, functionality can be limited, for example it can be set up to allow only certain people to edit data, to modify user privileges, or to run reports.

Chapter 26: Adverse Events

Adverse Event Reporting

An important consideration in a clinical study is the guidelines to be followed in case an adverse event occurs. Figure 26-1 represents the protocol to be followed in case of an adverse event. Reporting will be done in two different ways depending upon the severity of the event. The following criteria trigger an adverse event report:

1. The adverse event is serious (as defined below in accordance with Department of Health and Human Services (DHHS) definitions), or
2. The adverse event is not serious, but is unexpected and its association with the research-related procedure is either definitely, probably, possibly related, or unknown (as defined below).

DHHS Adverse Event Definitions

Adverse Event: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure; also an "unanticipated problem" of any nature (e.g., psychological or social harm) (designated as unrelated, definitely related, probably or possible related) (see definitions below).
Serious adverse event: Any adverse event that is fatal or life threatening, is permanently disabling (two line or more loss of best-corrected visual acuity), requires subject hospitalization or prolongs hospitalization, or results in a congenital anomaly or birth defect.
Life-threatening event: Any adverse event in which the subject is at immediate risk of death from the reaction as it occurs; does not include a reaction that, if it were to occur in a more serious form, might cause death.
Unexpected event: Any adverse event that is not identified in nature, severity, or frequency in the investigational brochure, study protocol, consent form, or IRB application; or the event was more serious than anticipated.

DHHS Adverse Event Associations

Definitely Related: An adverse event that has a timely relationship to the administration of the investigation procedure and follows a known pattern of response for which no alternative cause is present.
Probably Related: An adverse event that has a timely relationship to the administration of the investigation procedure and follows a known pattern of response, but for which a potential alternative cause may be present.
Possibly Related: An adverse event that has a timely relationship to the administration of the investigation procedure and follows no known pattern of response, but a potential alternative cause does not exist.
Unrelated: An adverse event for which there is evidence that it is definitely related to a cause other than the investigation procedure; in general, no timely relationship to the administration of the procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present.

The adverse event policy is not limited to adverse events resulting from investigation involving drugs, but also includes AEs involving any investigational device or research-related procedure. Federal policy [45 CRF 46.116(b) (5)] also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research. The IRB should receive copies of any such information conveyed to subjects. When an adverse event necessitates changes to the consent/assent form(s) and/or protocol, that notification is given to currently or previously enrolled subjects, and an amendment request should be submitted in conjunction with the adverse event report. The IRB will make a determination whether any new findings, new knowledge, or adverse events should be communicated to subjects.

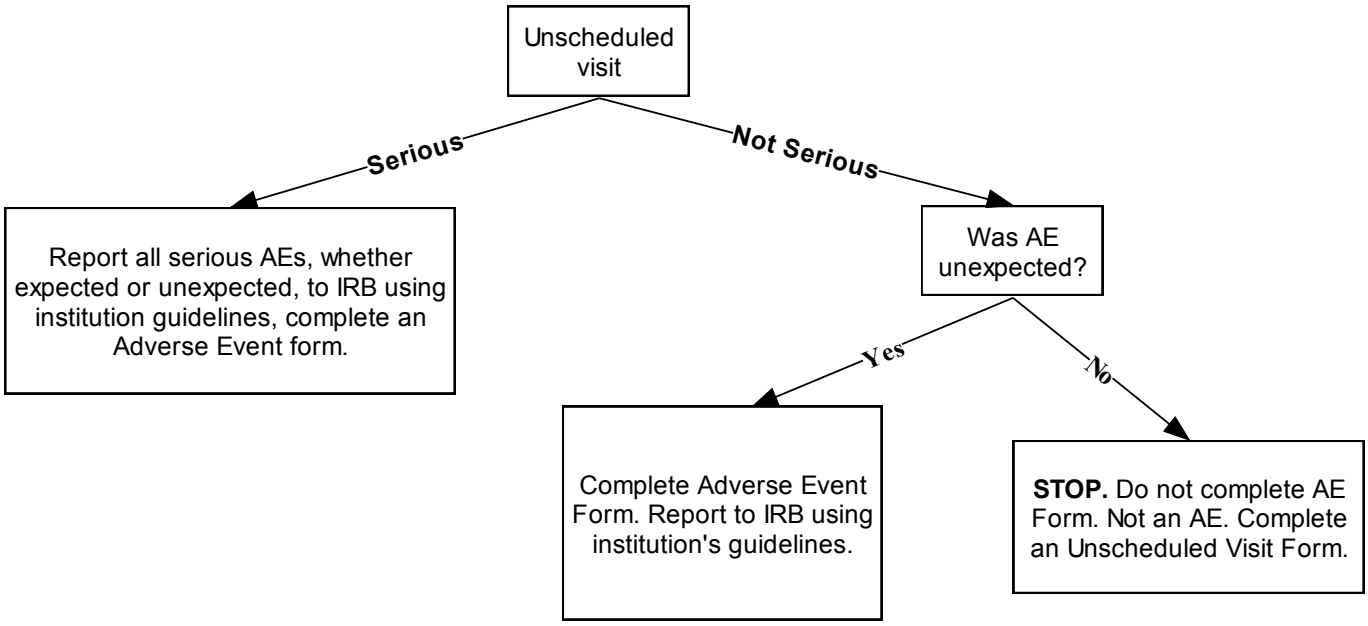
Although there is no universally accepted time requirement for reporting adverse events to the IRB, serious adverse events should be reported within 10 days of learning of the event. If the adverse event involved the death of a subject enrolled by an investigator, it should be reported immediately, usually within 48 hours. Note: deaths from "natural causes" or underlying disease that occur more than 30 days following completion of study interventions (i.e. events not temporally associated) need not be reported. Unexpected adverse events that are not serious but may be associated with the procedure should be generally reported to the IRB within 30 days of notification of the event (Figure 32-1).

In some instances, adverse events or "unanticipated problems" result in social or psychological harm rather than physical harm to subjects or others. These events should also be reported to the IRB within 30 days, unless they are considered "serious". A letter format may be used for reporting these events instead of the Adverse Event Reporting Form, as applicable.

Not all issues will trigger a subject presenting for an unscheduled visit, but may be still signal an undesirable outcome from contact lens wear (for example, headaches). An additional Event Report form will collect data on occurrences that are reported or solicited during a regularly scheduled visit.

Every event that triggers an unexpected visit requires the submission of an unscheduled visit form to the REDCap. Events on these forms are tabulated along with adverse events to determine if there are differences in the frequency of occurrence or severity of routine, expected events.

Figure 26-1. Flow chart for how to handle an adverse event



Determination of Adverse Events

There are three ways that an Adverse Event should be determined.

1. When a subject experiences ocular signs or symptoms worse than those encountered during routine contact lens wear. It is up to the examiner to determine when an Adverse Event Form should be completed.
2. At every visit, the examiner must ask the subject's parent or guardian, in these exact words, "Has your child experienced any changes in his or her eyes, vision, or health since the last visit?"

   All information that the parent expresses should be noted in the Other Examination Information box in REDCap. Whether or not an Adverse Event Form should be completed is determined by the examiner, after asking the appropriate follow-up questions.

   For example, if a parent says that her child had a headache, the examiner should ask the appropriate questions to determine the frequency, onset, location, duration, association, relief, and severity of the headache. After hearing the responses to the questions, the clinician should use his or her best judgment to determine whether or not this may be related to study treatment. If the examiner believes that it may be related to the study treatment, then an Adverse Event Form should be completed.
3. The examiner should ask the parent the precursor question about items in the Symptom Checklist, "Have you or your child noticed any of the following symptoms related to his or her eyes since the last visit?"

Each symptom should be read, and the parent should answer “yes” or “no” to each symptom. If the parent answers “yes,” then appropriate follow-up questions should be asked so that the examiner can determine whether or not the symptom may be related to the study treatment and therefore an Adverse Event Form should be completed.

In general, if the examiner is unsure of whether or not something should be categorized as an adverse event, then an Adverse Event form should be completed.

Chapter 27: Data Safety Monitoring Plan

As the proposed BAM Study is a K23 mentored career development award and it is not a clinical trial (the K23 mechanism does not allow for clinical trials), there will not be a formal Data Safety and Monitoring Committee (DSMC). However, the PI will participate in the annual DSMC meetings of the Bifocal Lenses In Nearsighted Kids (BLINK) Study, of which the proposed BAM Study will be an ancillary study. In addition, Drs. Walline (primary mentor of the BAM Study), Mutti (co-mentor), Jones-Jordan (collaborator for statistical analysis), and the PI will serve as an informal DSMC for the BAM Study to monitor data quality and subject safety. The PI and the mentors/collaborator will meet prior to study initiation to finalize plans for the conduct of research, at the end of recruitment, and at the end of each year of data collection to actively monitor study outcomes and discuss issues related to responsible conduct of research for the project. Additional meetings will be scheduled as needed. Adverse events and unusual events will be reported to the primary mentor Dr. Walline within 24 hours of the events. Adverse event forms and unusual event forms will be completed and reported to IRB using institution's guidelines.

All aspects of the study, including monitoring statistical analyses of study data for evidence of harmful, beneficial, or no treatment effects, will be monitored. Specifically, the PI and the mentors/collaborator will conduct the following duties at each meeting:

- Review the proposed study protocol, informed consent documents, assent documents, data management plans, and the plans for data and safety monitoring prior to the initiation of the study.
- Review data over the course of the study relating to recruitment, subject retention, protocol adherence, operating procedures, data form completeness, data quality, intervention effects, inclusion of both genders, minority inclusion, and subject safety.
- Identify safety-related issues during the course of the study.
- Propose appropriate analyses and periodically review safety and endpoints related to the study outcome.

At each meeting, consider the rationale for continuing the study with respect to recruitment, retention, protocol adherence, data management, safety issues, and outcome data. Based on current data, the PI and the mentors/collaborator will make a decision regarding the continuation of the study.

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