

blink

Bifocal Lenses In Nearsighted Kids

Manual of Procedures

Version 1.8: 5/31/18

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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.

Evidence from preliminary studies indicates that soft bifocal contact lenses with a distance center design slow myopia progression in children. It is hypothesized that they slow myopic eye growth by providing myopic defocus to the peripheral retina, which is a stimulus to slow eye growth. It is further hypothesized that the amount of peripheral myopic blur may be related to the amount of myopia control and the peripheral myopic blur primarily acts locally to slow peripheral eye growth. Determining whether these hypotheses are true could provide significant information about the regulation of eye growth that could optimize future myopia control devices and possibly lead to myopia prevention.

Chapter 2: Study Personnel and Organization

This list provides the name and role of each participant in the BLINK Study Group. Names are listed as they will be published, and the start and end dates indicate participation in the BLINK Study Group. This list will be updated by notifying the Study Coordinator.

| Executive Committee | | Start Date (mm/yy) | End Date (mm/yy) |
|--|-----------------------------------|--------------------|------------------|
| Jeffrey J. Walline, OD PhD | Study Chair | 9/2014 | |
| David A. Berntsen, OD PhD | Clinic Site PI | 9/2014 | |
| Donald O. Mutti, OD PhD | Clinic Site PI | 9/2014 | |
| Lisa A. Jones-Jordan, PhD | Data Coordinating Center Director | 9/2014 | |
| Donald F. Everett, MA | NEI Program Official | 9/2014 | |
| Chair's Center | | | |
| Jeffrey J. Walline, OD PhD | Study Chair | 9/2014 | |
| Kimberly J. Shaw, CCRP | Study Coordinator | 9/2014 | |
| Juan Huang, OD PhD | Research Faculty | 9/2014 | |
| Bradley E. Dougherty, OD PhD | Survey Consultant | 9/2014 | |
| Data Coordinating Center | | | |
| Lisa A. Jones-Jordan, PhD | Director | 9/2014 | |
| Loraine T. Sinnott, PhD | Biostatistician | 9/2014 | |
| Pamela Wessel | Project Coordinator | 9/2014 | 5/2017 |
| Jihuyn Lee, PhD | Research Programmer | 9/2015 | 9/2017 |
| Luke Bobay | Data Coordinator | 5/2017 | |
| Tina Opoku | Clinical Research Coordinator | 5/2018 | |
| University of Houston Clinic Site | | | |
| David A. Berntsen, OD PhD | Clinic Site PI | 9/2014 | |
| Laura Cardenas | Clinic Coordinator | 9/2014 | |
| Krystal L. Schulle, OD | Unmasked Examiner | 9/2014 | |
| Dashaini V. Retnasothie, OD MS | Unmasked Examiner | 9/2014 | 12/2015 |
| Amber Gaume Giannoni, OD | Masked Examiner | 9/2014 | |
| Anita Tićak Gostović, OD MS | Masked Examiner | 9/2014 | |
| Maria K. Walker, OD MS | Masked Examiner | 9/2014 | |
| Moriah A. Chandler, OD | Unmasked Examiner | 1/2016 | |
| Mylan Nguyen | Data Entry | 6/2016 | 8/2017 |
| Lea Hair | Data Entry | 5/2017 | |
| Ohio State University Clinic Site | | | |
| Donald O. Mutti, OD PhD | Clinic Site PI | 9/2014 | |
| Jill A. Myers | Clinic Coordinator | 9/2014 | |
| Alex D. Nixon, OD MS | Unmasked Examiner | 9/2014 | |
| Katherine M. Bickle, OD MS | Unmasked Examiner | 9/2014 | |
| Gilbert E. Pierce, OD PhD | Unmasked Examiner | 9/2014 | |
| Kathleen S Reuter, OD | Masked Examiner | 9/2014 | |
| Dustin J. Gardner, OD MS | Masked Examiner | 9/2014 | 9/2016 |
| Andrew D. Pucker, OD MS | Masked Examiner | 12/2015 | 7/2016 |
| Matthew Kowalski | Masked Examiner | 9/2016 | 5/2017 |
| Ann Morrison | Masked Examiner | 7/2017 | |

Data Safety and Monitoring Committee

| | | |
|-----------------------------|-------------|--------|
| Janet T. Holbrook, PhD | DSMC Chair | 9/2014 |
| Jane Gwiazda, PhD | DSMC Member | 9/2014 |
| Timothy B. Edrington, OD | DSMC Member | 9/2014 |
| John Mark Jackson, OD MS | DSMC Member | 9/2014 |
| Charlotte E. Joslin, OD PhD | DSMC Member | 9/2014 |

Chapter 3: Specific Aims

Hyperopic blur imposed solely on the peripheral retina causes rhesus monkey eyes to elongate excessively. Once the peripheral hyperopic blur is removed, foveal ablation does not derail emmetropization. This indicates that the peripheral retina is more important for regulating axial elongation than previously believed.

If peripheral hyperopic blur results in axial elongation, one predicts that peripheral myopic blur slows axial elongation. In fact, animal studies show that myopic blur is a stronger signal to slow axial elongation than hyperopic blur is to increase axial elongation. Soft bifocal contact lenses with a distance center design provide relatively more myopic defocus to the periphery than soft spherical contact lenses. This peripheral myopic defocus may slow axial elongation and myopia progression. In fact, non-randomized, short-term myopia control trials indicate that distance center design soft bifocal contact lenses slow axial elongation. One study used a contralateral eye study design, and the eye wearing the soft bifocal contact lens grew less than the eye wearing the soft spherical lens, even after switching treatment to the contralateral eye. Accommodation is yoked, so one expects myopia control due to change in accommodation to affect both eyes. Because axial elongation is always slower in the eye wearing a soft bifocal contact lens, evidence is strong that the peripheral myopic blur may be responsible. Another soft bifocal myopia control study found a correlation between axial elongation and the relative peripheral refractive error measured at 30° nasal and temporal and 40° temporal, again implicating peripheral refractive error in regulation of axial elongation. However, no long-term, randomized clinical trials have been conducted to definitively determine whether soft bifocal contact lenses slow myopia progression in children compared to single vision contact lenses over an extended time.

Furthermore, no study has conducted thorough measurements of the optics and shape the eye in order to determine how soft bifocal contact lenses may slow myopia progression. Measurement of peripheral defocus with the contact lens on the eye while looking at distance and near will provide a thorough assessment of the refractive error experienced by the eye. Comparison of the treatment effect between varying add powers of soft bifocal contact lens wearers and soft spherical wearers will determine whether the effect is primarily due to changes in eye shape or due to the contact lens itself. If greater peripheral defocus created by stronger add powers leads to differences in treatment effect, the contact lens is the primary determinant of myopia control, whereas if the relationship between peripheral defocus and myopia control is a greater determinant of myopia control than the amount of defocus, then eye shape is the primary determinant of myopia control. In addition to peripheral defocus, this three-year study will also examine the role of accommodative lag, pupil size, peripheral astigmatism, and the most myopic peripheral meridian in order to provide the most thorough assessment ever conducted of the optical profile and its effect on refractive error development.

Determining the role of peripheral defocus on the shape of the eye is also important for understanding how peripheral defocus may alter refractive error. Animal models indicate that hyperopic defocus results in longer eye lengths restricted to the corresponding retinal location. If this is the case in humans, peripheral myopic defocus produces slower peripheral growth than central growth. Comparing the change in both central and peripheral refractive error between soft bifocal and single vision contact lens wearers will help determine whether peripheral myopic defocus results in local changes in ocular shape or uniform changes in eye growth.

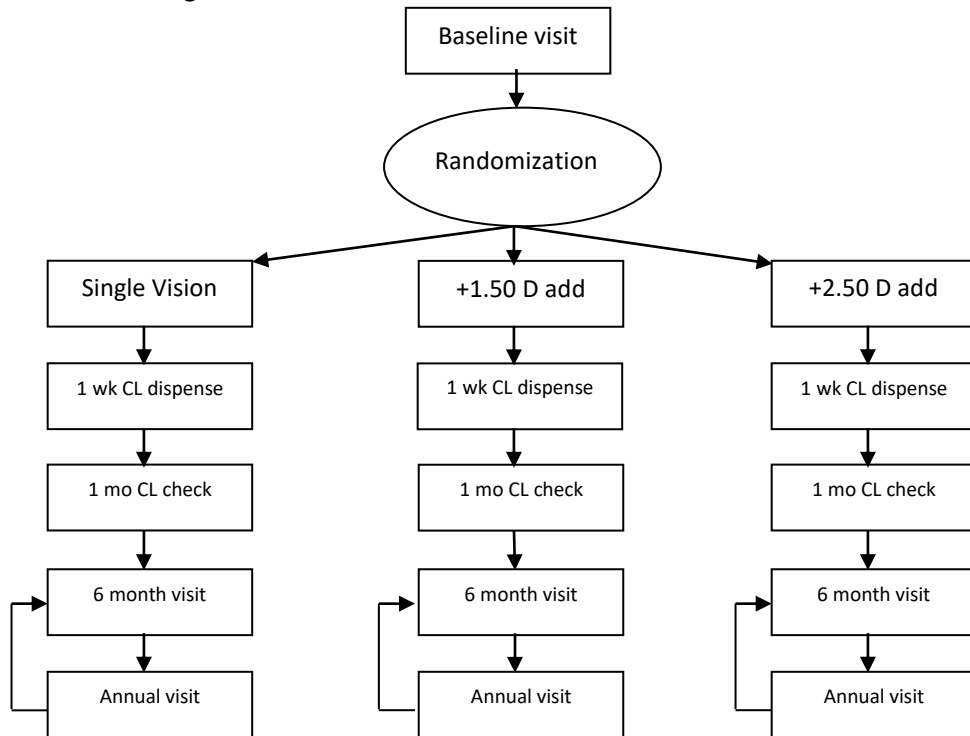
Data regarding whether greater peripheral myopic defocus slows myopia progression and how peripheral myopic defocus alters eye shape will provide crucial guidance toward optimizing the peripheral defocus signal in future contact lenses designed for myopia control and perhaps prevention of myopia onset. With a three-year randomized clinical trial of 294 myopic children between the ages of 7 and 11 years at baseline, we will accomplish the following specific aims:

- Specific Aim 1:** to compare the change in myopia between single vision contact lens wearers and soft bifocal contact lens wearers to test the hypothesis that soft bifocal contact lenses slow myopia progression in a dose-dependent manner in children,
- Specific Aim 2:** to determine whether peripheral defocus created by soft bifocal contact lenses is associated with myopia progression to test the hypothesis that peripheral myopic defocus slows myopia progression in children, and
- Specific Aim 3:** to determine whether changes in ocular shape differ between children wearing single vision and soft bifocal contact lenses to test the hypothesis that peripheral myopic defocus globally slows eye growth.

Chapter 4: Study Design

This is a multi-center, randomized clinical trial. Subjects will be randomly assigned to wear single vision contact lenses, soft bifocal contact lenses with a +1.50 D add, or soft bifocal contact lenses with a +2.50 D add for at least three years. Figure 4-1 illustrates the study schedule.

Figure 4-1: Flowchart illustrating the visit schedule and randomization.



Chapter 5: Sample Size

All sample size calculations were performed using PASS 2005 software using $\alpha = 0.05$ and $\beta = 0.10$ (power = 80%). Estimates of sample size were computed for each specific aim.

Specific Aim 1: to compare the change in myopia between single vision contact lens wearers and soft bifocal contact lens wearers to test the hypothesis that soft bifocal contact lenses slow myopia progression in a dose-dependent manner in children

Aim 1 is designed to compare myopia progression between two soft bifocal adds and single vision contact lens wearers using the mean value of the cycloplegic spherical equivalent (sphere + $\frac{1}{2}$ cylinder) as measured at one, two, and three years. These comparisons will be made using the common estimate of error obtained from a three group x three time point repeated measures analysis of covariance (ANCOVA), with the baseline spherical equivalent used as a covariate. To increase the efficiency of the F-tests performed as part of the ANCOVA, the total sample size will be equally allocated between the soft bifocal and single vision contact lens groups.

Sample size calculations are driven, in part, by the desired difference in spherical equivalent change between the three groups. This difference needs to be of a magnitude that is considered clinically relevant. Sample sizes are based upon the percent reduction in myopia progression between the two soft bifocal contact lens groups and the single vision contact lens group. Data used in the calculations are taken from the single vision contact lens group of the ACHIEVE Study, where the mean (\pm SD) myopia progression was $-1.29 \text{ D} \pm 0.71$ over three years (Walline et al., 2008). If we want to detect a 50% treatment effect (reducing the amount of myopia progression by roughly 0.65 D in the +2.50 D add group) and we estimate that the mean treatment effect for the +1.50 D add group is halfway between the single vision contact lenses and the +2.50 D add group (i.e., reducing myopia progression by 0.30 D in the second add), then the sample size required at 80% power is 24 per treatment group. Estimating the effect of the +1.25 D add group to be halfway between the two groups results in the largest sample size possible (a conservative estimate). Should we find that both adds have a similar effect, we will be more than adequately powered. If we look at a reduction of 0.50 D (a treatment effect of 40% in the highest add group), then the sample size is 40 per treatment group at 80% power. A 30% treatment effect (a reduction of about 0.40 D in the amount of myopia progression in the +2.50 D add group) yields a sample size of 62 subjects per treatment group.

Specific Aim 2: to determine whether peripheral defocus created by soft bifocal contact lenses is associated with myopia progression to test the hypothesis that peripheral myopic defocus slows myopia progression in children

Analysis of the relationship between the amount of peripheral defocus and the amount of myopia progression will provide information on how the level of peripheral defocus may affect the progression of myopia. That is, are higher levels of peripheral myopic defocus associated with a decreased rate of foveal myopia progression? Peripheral defocus is measured in this study at multiple locations (20°, 30°, and 40°) in two gaze positions (nasal and temporal). The association between peripheral defocus and myopia progression will be assessed using a correlation analysis and linear regression. Based on recent work by Sankaridurg et al. (2011), a clinically meaningful magnitude of correlation between peripheral defocus and myopia progression is 0.25. To detect a correlation as small as 0.25 at 80% power would require 123 subjects total.

Specific Aim 3: to determine whether changes in ocular shape differ between children wearing single vision and soft bifocal contact lenses to test the hypothesis that peripheral myopic defocus globally slows eye growth

Aim 3 is designed to evaluate differences in the change in ocular shape between the two soft bifocal and single vision contact lens groups using the measure of relative peripheral refractive error across the horizontal and vertical meridians of the eye. Relative peripheral refractive error is computed by subtracting the central cycloplegic spherical equivalent autorefraction from the peripheral spherical equivalent autorefraction, each measured with no refractive

error correction. Analyses will use a repeated measures ANCOVA with gaze direction and fixation as within-subject factors. To increase the efficiency of the F-tests performed as part of the ANCOVA, the total sample size will be equally allocated between the soft bifocal and single vision contact lens groups.

Sample size estimates are based upon a magnitude difference of the change in “ocular shape” between the single vision contact lens and the +2.50 D add bifocal treatment groups of 0.40 D. In order to ensure that we have adequate sample size to find a true difference, we have made the assumption that the +1.50 D add bifocal group will experience a change that is intermediate between the other two groups (i.e., 0.20 D). Making this assumption gives us a conservative estimate of sample size (i.e., the maximum sample size). While no longitudinal data assessing the amount of change in periphery that can be considered clinically meaningful, it is reasonable to assume that a clinically meaningful change in the center would be considered a clinically meaningful change in the periphery as well. As such, we know that the minimal difference in central refractive error change that has been detected in previous studies is 0.13 D over one year. If this amount of difference in refractive error change continues for three years, then the minimal meaningful difference would be 0.39 D, which we rounded to a 0.40 D difference. The standard deviation arises from the Study of Theories about Myopia Progression, and is set at 0.85, which represents the most conservative standard deviation in the change in relative peripheral refraction seen across measures. Using this information the sample size required to detect this magnitude of difference in the change in ocular shape between treatment groups with 80% power is 89 subjects per group, for a total sample size of 267 subjects.

Sample Size Conclusion

Table 5-1 provides a summary of the sample size requirements based on the three study aims. Although we strive to retain all subjects, the sample size will be adjusted to account for a possible 10% loss to follow-up. This is a reasonable expectation. Dr. Berntsen, when at Ohio State, had a retention rate of 98% in his Study of Theories about Myopia Progression clinical trial, and other clinical vision studies conducted at the University of Houston have retention rates exceeding 90%. Likewise, Dr. Walline’s experiences at Ohio State with ACHIEVE (OSU clinic saw 100% of subjects for final visit) and the Contact Lens and Myopia Progression trial (100% of subjects at final visit) indicate that a 10% loss to follow-up is an acceptable assumption. Using the maximum sample size from Table 5-1 (n=267) and adjusting for 10% loss to follow-up gives a **total sample required of 294** (98 children assigned to each treatment group).

Table 5-1: Total sample size required at 80% power in the Soft Bifocal Contact Lens Myopia Control Study

| Aim | Total sample |
|----------------------|--------------|
| Specific Aim 1 | |
| 50% treatment effect | 72 |
| 40% treatment effect | 120 |
| 30% treatment effect | 186 |
| Specific Aim 2 | 123 |
| Specific Aim 3 | 267 |

Chapter 6: Timeline

During the first six months of funding, preparation for the trial will begin. The DSMC will meet as early as possible (after preparation of study forms and DSMC binders) in order to finalize the protocol. Once the protocol is finalized, certification of examiners will begin at the FIG meeting, both near the end of the initial six-month period.

Recruitment will begin at the beginning of month seven and continue for 15 months. All follow-up visits will begin within one week of the first subject visit. The last one-year, two-year, and three-year visits are expected to be complete within one month of the anniversary date of the last subject enrolled.

The DSMC will meet annually, after recruitment and each year of follow-up is complete and the data are analyzed. FIG meetings will be held after each DSMC meeting in order to update protocols, motivate investigators, and discuss problems encountered. Writing groups will also meet during the FIG meetings.

A baseline manuscript describing the sample, methods, and vision of subjects fit with the +2.50 D add for inclusion criteria will be written when enrollment is complete. When 75% of the subjects have completed the trial, a draft of the primary outcome manuscript will be written. The draft will be shared with the DSMC for approval. When the study is complete, data will be finalized, the entire study group will provide comment prior to submission, and the DSMC will provide final approval. The complete study timeline is shown in Figure 6-1.

Figure 6-1: Timeline for conduct of the Soft Bifocal Contact Lens Myopia Control Study.

| Years | Year 1 | | | | Year 2 | | | | Year 3 | | | | Year 4 | | | | Year 5 | | | |
|-----------------|--------|-----|-----|-------|--------|-------|-------|-------|--------|-------|-------|-------|--------|-------|-------|-------|--------|-------|-------|-------|
| Months | 1-3 | 4-6 | 7-9 | 10-12 | 13-15 | 16-18 | 19-21 | 22-24 | 25-27 | 28-30 | 31-33 | 34-36 | 37-39 | 40-42 | 43-45 | 46-48 | 49-51 | 52-54 | 55-57 | 58-60 |
| Preparation | | | | | | | | | | | | | | | | | | | | |
| Certification | | | | | | | | | | | | | | | | | | | | |
| Recruitment | | | | | | | | | | | | | | | | | | | | |
| Follow-up | | | | | | | | | | | | | | | | | | | | |
| Data analysis | | | | | | | | | | | | | | | | | | | | |
| DSMC | | | | | | | | | | | | | | | | | | | | |
| FIG meetings | | | | | | | | | | | | | | | | | | | | |
| Manuscript prep | | | | | | | | | | | | | | | | | | | | |

Milestone events throughout the study will be scheduled according to the first day of funding. Table 6-2 lists those dates in order to help with goal setting and planning.

Table 6-2: An April 1, 2014 funding date initiates the following events.

| Month | Event |
|-------------------|---|
| April 2014 | Entry of the clinic trial into clinicaltrial.gov |
| April - July 2014 | MOP and forms drafts |
| June 2014 | DSMC suggestions for MOP and forms |
| July 2014 | Version 1 of MOP and forms completed |
| July 2014 | FIG meeting in Columbus |
| August 2014 | Prepare clinics and recruitment materials |
| August 2014 | Site Visits |
| August 2014 | Recruitment begins |
| July 2015 | Recruitment ends |
| September 2015 | DSMC meeting |
| September 2015 | Baseline manuscript submitted to Optometry and Vision Science |
| October 2015 | FIG meeting in Houston |
| November 2015 | Site Visits |
| September 2016 | DSMC meeting |

| | |
|----------------|---|
| October 2016 | FIG meeting in Columbus |
| November 2016 | Site Visits |
| September 2017 | DSMC meeting |
| October 2017 | FIG meeting in Houston |
| November 2017 | Site Visits |
| August 2018 | Last subject completed |
| September 2018 | DSMC meeting |
| September 2018 | FIG meeting in Columbus |
| September 2018 | Submit primary outcome paper to JAMA (Aim 1) |
| November 2018 | Submit peripheral myopic defocus and myopia progression paper to IOVS (Aim 3) |
| February 2019 | Submit eye shape and contact lens correction paper to Vision Research (Aim 3) |

Chapter 7: Eligibility

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

| | |
|------------------|---|
| Age | 7 to 11 years, inclusive, at baseline examination |
| Myopia | -0.75 to -5.00 D, inclusive, spherical component, cycloplegic autorefraction in each eye |
| Astigmatism | ≤1.00 DC, cycloplegic autorefraction in each eye |
| Anisometropia | ≤2.00 D, spherical component, cycloplegic autorefraction in each eye |
| Visual acuity | +0.1 logMAR or better best-corrected distance visual acuity in each eye <i>AND</i> +0.1 logMAR or better best-corrected, binocular, high contrast visual acuity at distance with +2.50 D add soft bifocal contact lenses on both eyes |
| Contact lens fit | The +2.50 D add soft bifocal contact lens must provide adequate movement and centration for continual wear |
| Ocular health | Free of eye disease or binocular vision problems (eg, strabismus, amblyopia, corneal disease, etc.) that may affect vision or contact lens wear |
| Systemic health | Free of systemic disease that may affect vision, vision development, or contact lens wear (eg, diabetes, Down syndrome, etc.) |
| Contact lens | By patient report, not more than one month of gas permeable, soft bifocal, or orthokeratology 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 |
| Medications | No chronic use of medications that may affect immunity, such as oral or ophthalmic corticosteroids |
| Participation | Agree to participate in the study for three years |

Eligibility will be confirmed by the Data Coordinating Center using the eligibility module in the REDCap electronic data capture system. When eligibility has been confirmed, subjects will receive a randomization assignment through the randomization module.

If a subject is ineligible, the Study Completion Form should be completed in REDCap with the reason for the ineligibility.

Chapter 8: Outcome Measures

There are nine scheduled visits during the BLINK 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 8-1.

Table 8-1: 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 8-2. The masked examiner will measure the primary outcome in both eyes at baseline and annually thereafter. The masked examiner will perform all central and peripheral autorefractometry and eye length measurements during which the subject is contact lens-free. The masked examiner will not perform other outcomes because measurement of the outcome would reveal the treatment group.

Table 8-2: Schedule of measurements for the study. Cycloplegic autorefractometry 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 |
| Non-cycloplegic autorefractometry (OU) | X | | | X | X |
| Manifest refraction (OU) | | | | | X |
| Accommodative Lag with Manifest (OD) | X | | | | |
| Cycloplegic autorefractometry (1° outcome, OU)* | X | | | | X |
| Peripheral refractive error without CL (OD)* | X | | | | X |
| Axial length (OU)* | X | | | | X |
| Peripheral eye length (OD)* | X | | | | X |
| Aberrations with and without CL (OD)* | | | | | Visit 5 only |
| Peripheral defocus with CL (OD)* | X | | | | X |
| Intraocular pressure (OU)* | X | | | | X |
| Dilated fundus examination (OU)* | X | | | | X |
| Contact Information Form | X | | | | X |
| History Form | X | | | | |
| Myopia Risk Factor Form | X | | | | |
| PREP2 Form | | | X | X | X |
| CISS Form | X | | X | Visit 4 only | X |
| Contact Lens Form | | | X | X | X |
| Parent Compliance Form | | | X | X | X |
| Insertion, Removal, and Care Training | | X | | | |
| Length of visit (hours) | 2.0 to 2.5 | 1.0 | 0.75 | 0.75 | 2.0 |

■ = masked measure; CL = contact lens; * = 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, across the three treatment modalities.

We will measure the axial length, 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.

Subjects will complete a PREP2 survey at Visits 3 through 9 to compare satisfaction with vision correction between soft bifocal and soft spherical contact lenses. Subjects will not complete the PREP2 at Visits 1 or 2 because they are not required to be wearing myopic correction at these visits. All subjects will complete a compliance survey at Visits 3 through 9 in order to determine whether compliance with contact lens is associated with myopia control effects or differs by treatment group.

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 20 minutes. Achieving cycloplegia requires 30 minutes, and the cycloplegic portion of the examination at Visits 1, 5, 7, and 9 requires approximately 50 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 to 2 ½ hours, which is similar to baseline examinations for the STAMP, CLAMP, and CRAYON studies. Annual examinations will require approximately 2 hours to complete because informed consent will not be conducted and because subjects are much less nervous about participation. 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 also moved dispensing of contact lenses and the contact lens care training from Visit 1 to 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 9: 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 9-1). If the subject passes the phone screen, a Visit 1 appointment should be scheduled.

Table 9-1: 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 allow your child to be randomly assigned to a treatment? | 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. Once eligibility is confirmed, the subject's randomized treatment assignment will be determined.

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.

The timing of all visits will be based on the date of randomization. The window for Visits 4 through 9 opens one month before the anniversary date and closes one month after the anniversary date. The clinic receives notification when the window opens, and when the window closes without receipt of study forms by the Data Coordinating Center (DCC). The window for Visit 2 opens 1 day before and closes 1 day after the one week visit date, and the Visit 3 window opens one week before and closes one week after the 3 week date.

Eligibility data will be transmitted to the Data Coordinating Center after completion of the cycloplegic autorefractometry. Eligibility criteria will be reviewed by the web-based system. If the subject data satisfy all criteria, the randomization assignment is provided immediately. The subject will be randomly assigned to one of the three treatment groups. A log of all entered and transmitted data is kept at the Data Coordinating Center for data integrity and quality control review.

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, and
- subject initials.

The clinic designations and range of subject identification numbers follows:

| Institution | ID numbers |
|-------------|------------|
| OSU | 001 – 399 |
| UH | 401 – 799 |

For example, subject ID "404-TJ" is the fourth subject enrolled at the Houston clinic, 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 receiving the randomization assignment. 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 9-2.

Table 9-2: 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 and/or the Coordinator will address those questions as appropriate. If these calls involve eye care matters, the appropriate subject care team member 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. A copy of the adverse event form should be forwarded to the DCC.

Late Visits and Searches for Missing Subjects

The DCC will send a notice to the clinic sites one month prior to the opening of the subject's visit window. If the DCC does not receive study forms back within one month of the expected visit date, a late visit form will be sent to the site requesting information about that late visit. All late visit forms will be forwarded to the Chair's Office by the DCC. If the clinic site indicates their search for the subject has been unsuccessful, the Chair's Office will initiate a subject search. That search will include calls, mailings, and the use of subject locator services.

Recruitment

Recruitment methods that are most appropriate for each clinical site will be used. They 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 baseline visit.

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.

Crossovers

As a tenet of the informed consent process, subjects are able to withdraw from a study or switch treatments at any time. The fact that subjects are allowed to switch treatment groups if they desire should not be advertised. A subject will only be allowed to switch treatment groups if that is the last remaining option for keeping the subject in the study.

For example, 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. If there are any irregularities in the case or if there are questions, contact the Study Chair.

Discontinuation

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 subject may be examined at the other clinic site or the Chair's Office may pay 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 Clinic PI and Study Chair.

If a subject cannot be located, and the clinic site has exhausted all potential contacts, the Chair's Office will conduct a professional search using alternative resources. Contact the Chair's Office as soon as the clinic site determines that they are not able to locate the subject.

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 10: Informed Consent

Introduction

The Unmasked Examiner is usually the person responsible for explaining the study to potential subjects and for insuring that the informed consent process is appropriately completed. Particularly because the study involves randomization, explanation of the nature of the study is important. 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.

Each participating clinical site is responsible for obtaining IRB approval from their institution for this clinical trial. Copies of the IRB approval should be sent to the Chair's Office each year to ensure the sites remain IRB compliant.

Study Population

The subject sample in the clinical trial 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; the Data Coordinating Center receives no personal identifier information, only a subject identification number. 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 1 (2.0 to 2.5 hours): informed consent, comprehensive vision examination, visual acuity, pupil size measurement, slit lamp examination, axial length measurement, 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 hour): slit lamp examination and insertion, removal, and care training.

Visit 3 (0.75 hours): visual acuity, slit lamp examination, accommodative lag, and surveys.

Visits 4, 6, and 8 (0.75 hours): slit lamp examination, visual acuity, and completion of study surveys.

Visits 5, 7, and 9 (1.5 hours): comprehensive vision examination, visual acuity, pupil size measurement, slit lamp examination, axial length measurement, cycloplegic autorefraction, peripheral autorefraction with and without the contact lens, peripheral eye length, 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)

All subjects will receive free comprehensive eye care, reduced cost for glasses, 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 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 clinics in Houston, TX and Columbus, OH which will provide a representative sample of young myopes.

Chapter 11: Randomization

Subjects who meet the entry criteria will be randomly assigned to single vision, soft bifocal with +1.50 D add, or soft bifocal with +2.50 D add contact lenses for at least three years. The randomization assignment will be conducted through REDCap, the web-based, electronic data capture system that also verifies the eligibility of the subject. The randomization assignment will be stratified by clinical site and age, using a random permuted block design to ensure sequential balance of the distribution of the three treatments among the age groups and clinic sites. A child is considered enrolled once the randomization assignment and study identification number are received. When the randomization assignment is received from the web site, the investigator should complete the Randomization Form. The Randomization Form should not be sent to the Data Coordinating Center, it should be maintained in the subject's study binder.

Chapter 12: Masking

This will be a double-masked study. Subjects will not know the contact lens modality to which they are allocated. Contact lens boxes will be eliminated, and all contact lens brandings will be de-identified prior to dispensing. At no point during the study will the subjects be told their treatment assignment. There are no identifying marks on the contact lenses that would help subjects identify their treatment. All contact lens care will be similar, regardless of contact lens modality.

Masked examiners will perform masked measurements at the baseline and annual visits. The masked examiners will not be allowed in the clinical area, other than to perform their masked examination duties. The masked examiners will never examine the subjects while they are wearing contact lenses. All contact lens cases, packages, and solutions will be placed in a hidden location during the masked portion of the examinations, and subjects will be told not to discuss their contact lens wear or care with the masked examiner.

Four outcomes will be conducted by an examiner who is masked to the assigned treatment group.

- Cycloplegic autorefractometry (OU)
- Axial length (OU)
- Peripheral refractive error without a contact lens (OD)
- Peripheral eye length (OD)

Assessment of Masking

We will monitor both subject and masked examiner masking at each annual examination by asking the following questions:

1. How sure are you of whether you are / the subject is wearing bifocal or non-bifocal contact lenses?
 - a. Very sure
 - b. Sure
 - c. Unsure
 - d. Very unsure
2. What contact lenses do you think you are / the subject is wearing?
 - a. Bifocal
 - b. Non-bifocal
3. If you are 'very sure' or 'sure,' why do you think that?
 - a. Something I overheard
 - b. Something I saw on the contact lens
 - c. Something I saw on the packaging
 - d. A study result that I saw
 - e. Other: _____

We will monitor the results to determine whether unmasking possibly occurred by assessing the proportion of correct guesses to question 2 if subjects or masked examiners say that they were 'very sure' or 'sure' to question 1. We will also assess responses to question 3 for all of the correct guesses to question 2 if they said 'very sure' or 'sure' to question 1. This will help to eliminate potential sources of unmasking. The masking results will also be published in the primary outcome manuscript.

Chapter 13: Visual Acuity

Performed By

Unmasked Examiner

Eyes

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

Equipment

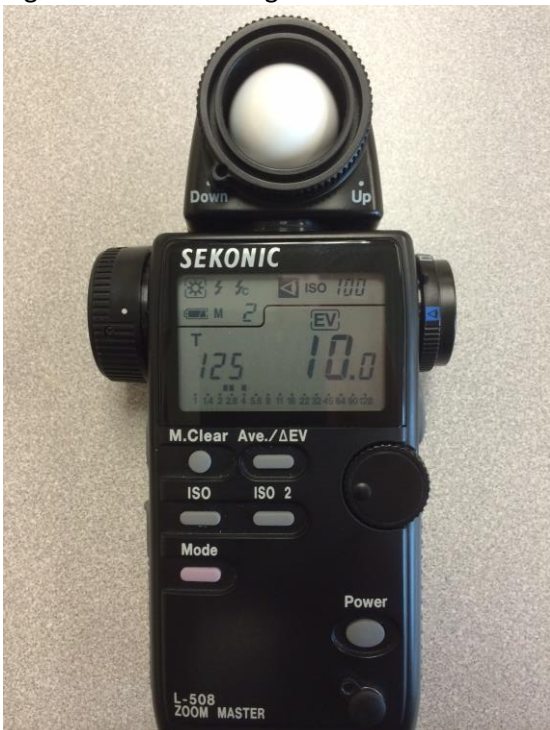
Bailey-Lovie logMAR high contrast charts #4 and #5, and low contrast visual acuity chart #6 (UC Berkeley School of Optometry, Berkeley, CA) are used. Test distances of 6 meters, 4 meters, and 2 meters must be clearly marked. The Sekonic L-508 Zoom Master (Sekonic, Tokyo, Japan) light meter will be used.

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.

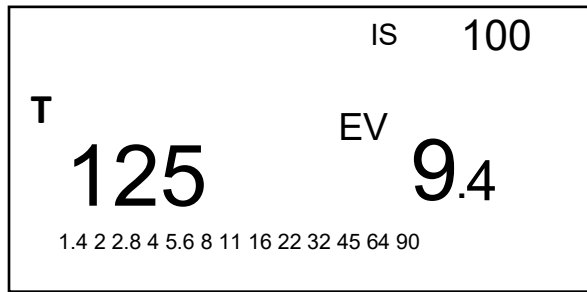
1. Press the [Power] button, and the LCD display will illuminate.
2. Turn the lens knob on the left of Figure 13-1 to the smallest white spot.
3. Turn the eye piece on the right so the pointer points to the blue square (Figure 13-1).
4. Turn the knob on the right, below the LCD display, until 125 appears in the lower left of the screen (Figure 13-1).
5. The number 100 should be displayed on the top, right (Figure 13-1).
6. Point the white orb on the top of the meter to you (Figure 13-1).

Figure 13-1: Sekonic light meter.



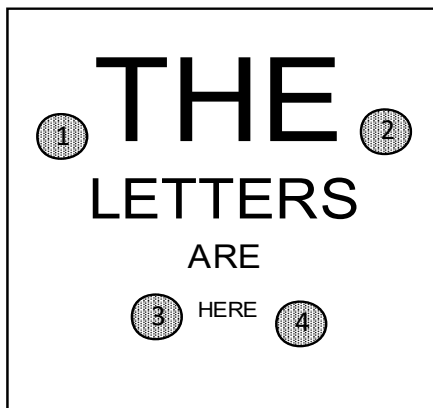
At this point, the LCD display should look like Figure 13-2, except the number to the right of EV may not be 9.4 (it can be anything at this point).

Figure 13-2: 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 13-3: 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.

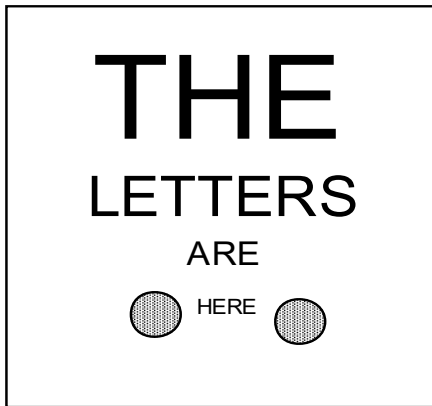
1. Stand the subject at the mark located 4 meters from the chart.
2. Instruct the subject to read the first letter on each line, continuing down the chart until the first letter is missed.
3. Start two lines above the missed letter.
4. Tell the subject to read five letters from every line. If the subject 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 13-4.
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 13-4: 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 or phoropter 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 14: Modified Thorington

Performed By

Unmasked Examiner

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

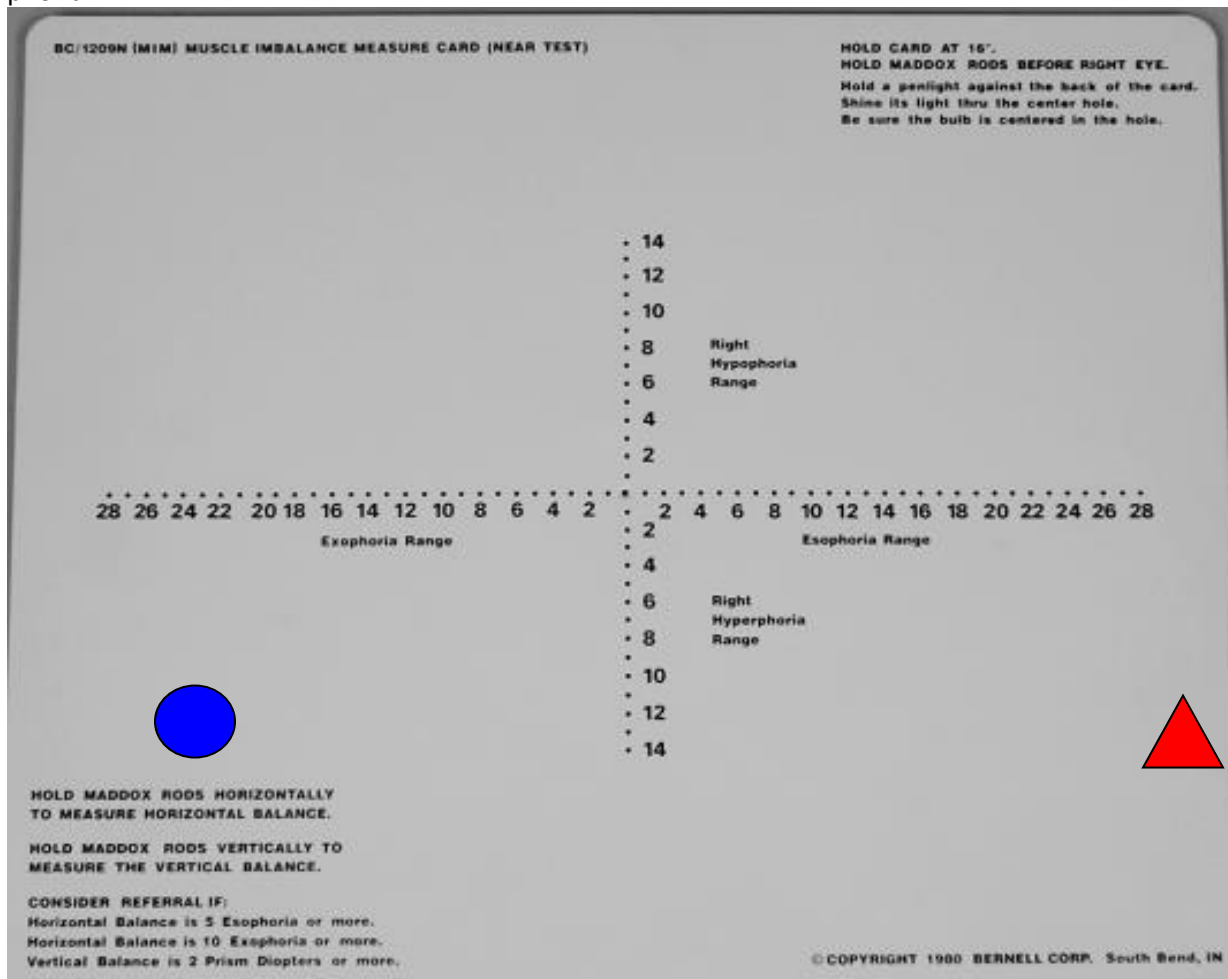
- Maddox Rod
- Muscle Imbalance Measure (MIM) near card
- Pen light

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 14-1).
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 14-1: 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 14-1). Take care not to tilt or rotate the prism. The prism should be held close to the eye (spectacle plane).

Table 14-1: 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 15: Accommodative Lag and Peripheral Defocus With Contact Lens at Near

Performed By

Unmasked Examiner

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 ±20°, ±30°, and ±40° from the line of sight. (Note: No measurements will be made at ±10°, and these slots should be filled to prevent accidentally placing a target in these locations).

Measurement Procedure

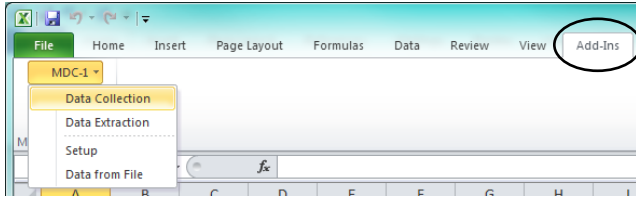
These measurements are performed by an unmasked examiner on the right eye only with normal accommodation (i.e., NO cycloplegia). Left and Right refer to the direction the subject looks. A picture of the autorefraction horizontal target holder tray (examiner side) is shown in Figure 15-1.

Figure 15-1: autorefraction horizontal target holder tray, viewed from the examiner's side.



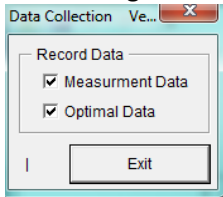
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated as COM3).
2. Navigate to the peripheral autorefraction Excel Template file (PeripheralAuto_Template.xlsx) located in the "BLINK Templates" folder 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 15-2).

Figure 15-2: Click on the Add-Ins tab in Excel.



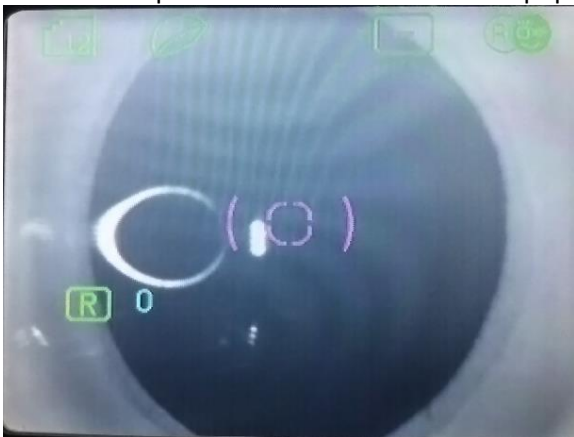
- Once the Grand Seiko successfully connects to the laptop, you will see the window in Figure 15-3.

Figure 15-3: Signifies successful connection to laptop.



- Place an eye patch over the subject's left eye.
- 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.
- Place the 33cm near rod in the appropriate slot to measure with the subject looking 40° to his/her left (nasal retina). *Verify that the target is located at the 33cm mark on the rod!*
- 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.
- 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.
- 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 15-4).

Figure 15-4: 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 30° Left (30L), 20° Left (20L), Central (0°), 20° Right (20R), 30° Right (30R), and 40° Right (40R).
(Note: It is important that you always follow this order – 40L, 30L, 20L, Central, 20R, 30R, 40R. 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 16: Slit Lamp Examination

Performed By

Unmasked Examiner

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. An adverse event report should be completed when a subject experiences ocular signs or symptoms worse than those encountered during routine contact lens wear.

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 17: Pupillometry

Performed By

Unmasked Examiner

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, 5, 7, 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/m² 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 18: Choroidal Thickness

Performed By

Unmasked Examiner

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

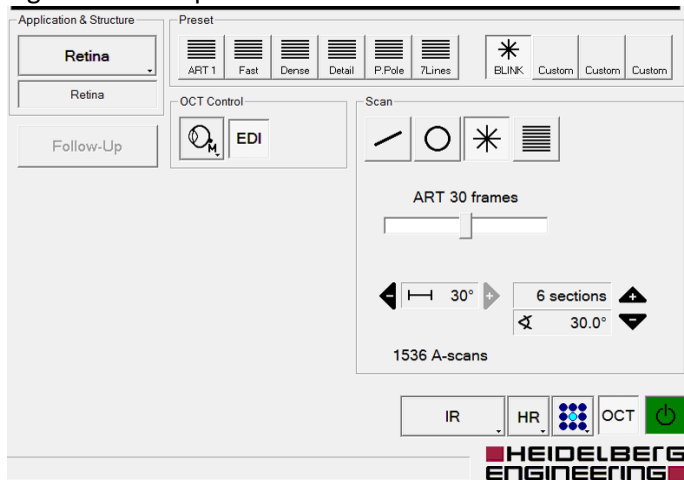
Studies have reported changes in choroidal thickness in response to optical defocus. We will investigate whether changes in choroidal thickness occur over in the control and treatment groups. OCT images will be collected through a non-dilated pupil. Because choroidal thickness changes have been reported 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 18-1):


- 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 18-1: 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 18-2a).
- b. Press the "More" button in the upper right corner. On the next screen, press the "Auto" button under the Image Brightness section (Figure 18-2b).

Figure 18-2: Touch pad buttons to push.

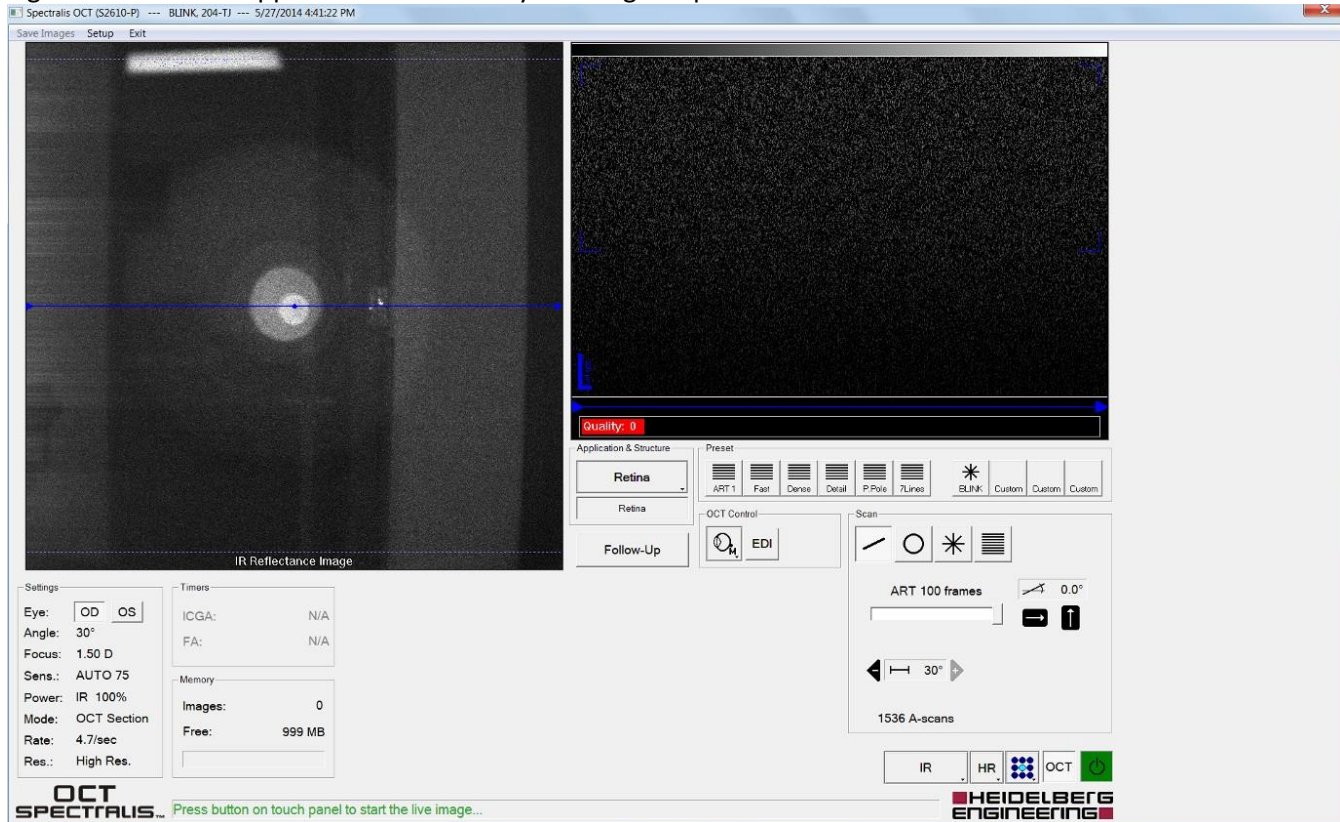


18-2a

18-2b

After completing these steps on the touch pad, the computer monitor will look as shown in Figure 18-3.

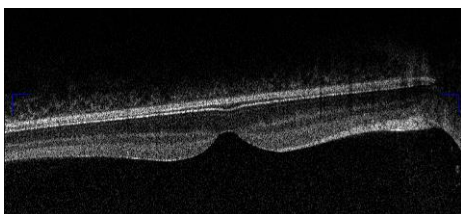
Figure 18-3: Screen appearance when ready for image acquisition.



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 18-10).

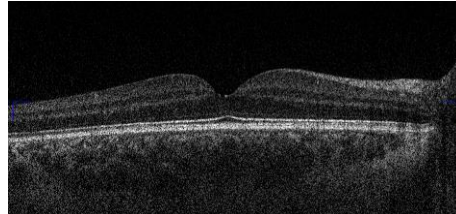
(Note: Moving in and out will adjust the vertical position of the OCT image. If you push in too far, the image flips so that the choroid is on top and the retina is on bottom; if this happens, pull the instrument back.)

Figure 18-4a



Upside down
(pull instrument back!!!)

Figure 18-4b



Correct orientation
Retina on top, choroid on bottom

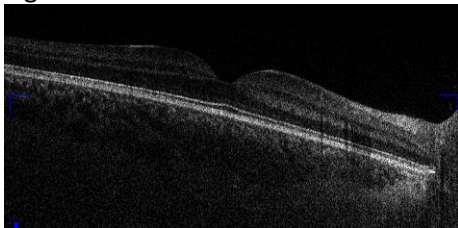
9. Focus the IR Reflectance Image by turning the focus knob (Figure 18-5) on the OCT head counterclockwise (which adds plus) until it is blurry, and then clockwise (which adds minus) until the fundus image and vasculature in the IR Reflectance Image window first looks clear. Note: the focus amount should 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 18-5: Focus knob.



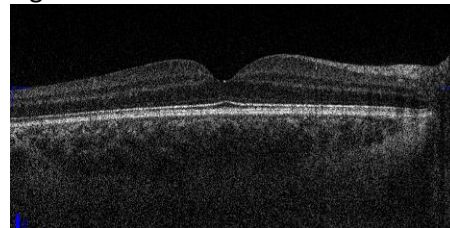
10. Move the OCT head left and right to flatten the OCT b-scan image AND until you have maximized image signal on the right and left side of the b-scan (Figures 18-6a-c). (Note: Very subtle tilting of the b-scan is sometimes needed to maximize image signal across the entire b-scan.) The bold blue line 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 18-6a



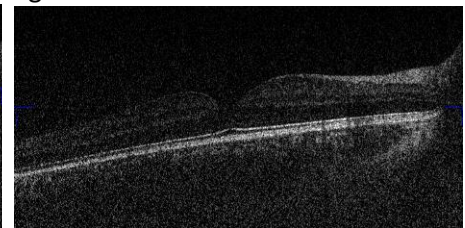
Not flat (tilted)
Image signal reduced on one side

Figure 18-6b



Flat (good)
Image signal uniform across b-scan

Figure 18-6c



Not flat (tilted)
Image signal reduced on one side

11. Click the button labelled “BLINK” in the Preset area (Figure 18-7). 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 18-7: Preset area. Note the “BLINK” button below the right image (see arrow).



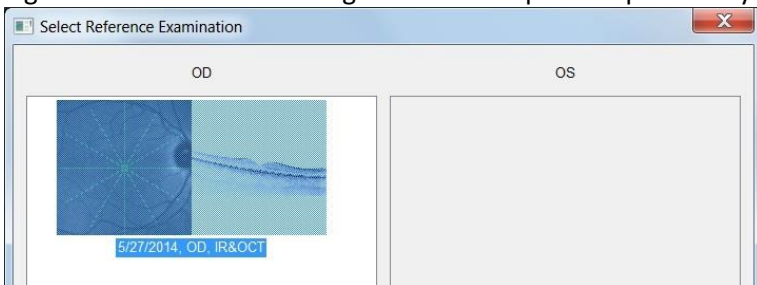
12. Be sure that the OCT b-scan image is centered vertically within the window and is flat with good image signal across the b-scan, and then activate the eye tracking mode:
 - a. Visit 2: Activate the eye tracker by pressing the black gain control button (Figure 18-8) on the touch pad. (Note: If you 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 18-8: Note the round, black gain control button.



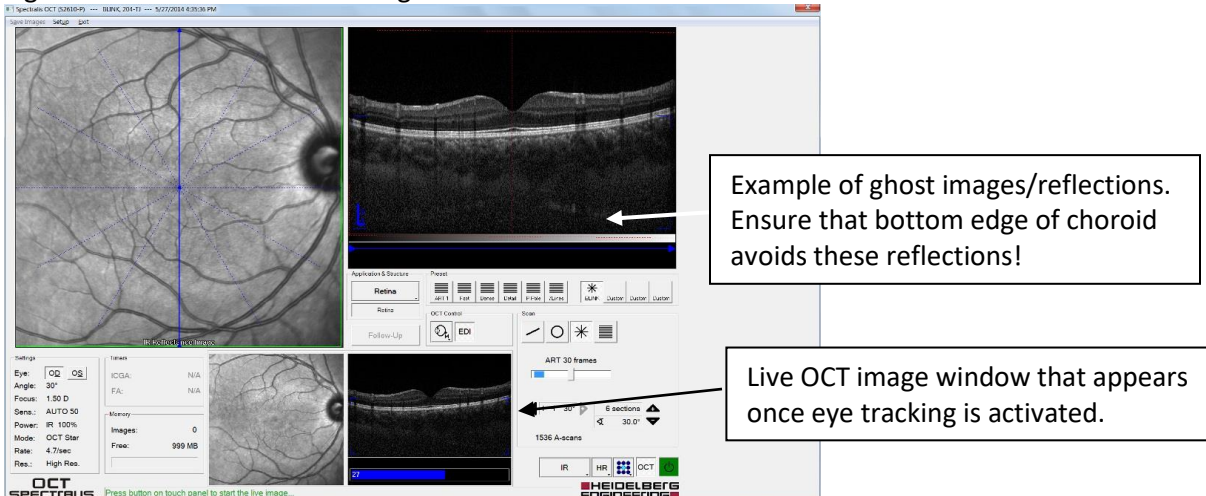
- b. All Visits after Visit 2: Click the "Follow-Up" button using the mouse. This mode maximizes instrument repeatability. Select the baseline image from reference examination the list (Figure 18-9, only one exam should be available to pick) and click OK. The eye tracker is now activated. (NOTE: If the "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 18-9: 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 18-10: 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.

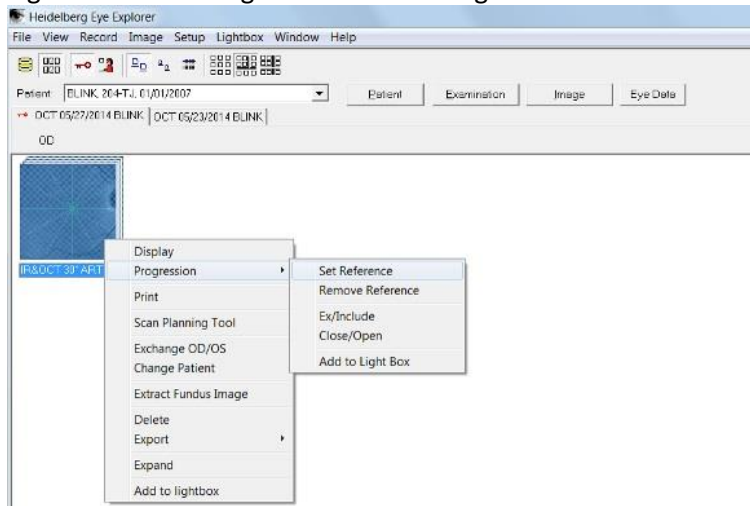
16. Upload E2E file to RedCAP. (See OCT export and upload section below.)

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:

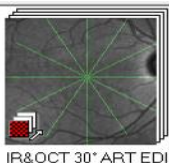
1. Select the best scan acquired at Visit 2 to use as the reference image. Right click on the baseline OCT scan thumbnail (Figure 18-11), select “Progression” and then select “Set Reference”

Figure 18-11: Setting the reference image.



2. A red and black square can now be seen in the bottom left side of the thumbnail (Figure 18-12) indicating that it is a reference image that can be selected when using Follow-Up mode at return visits.

Figure 18-12: Reference image.

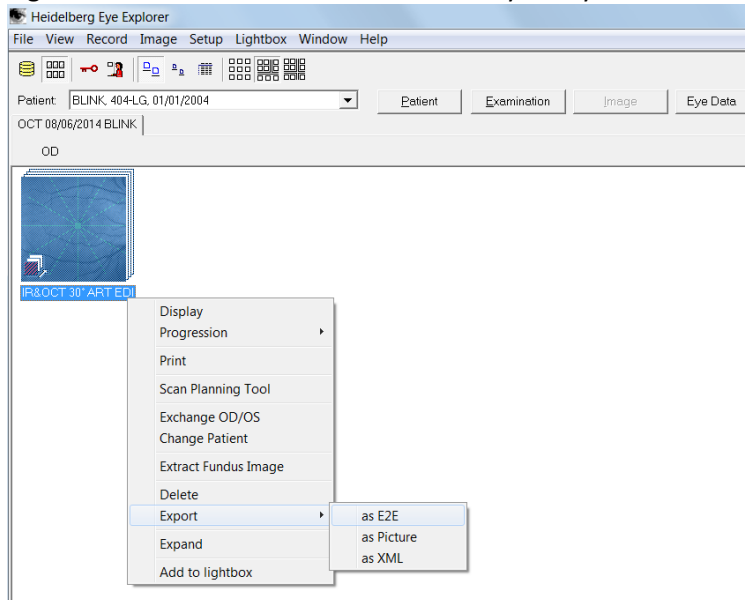


OCT Export and Upload

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

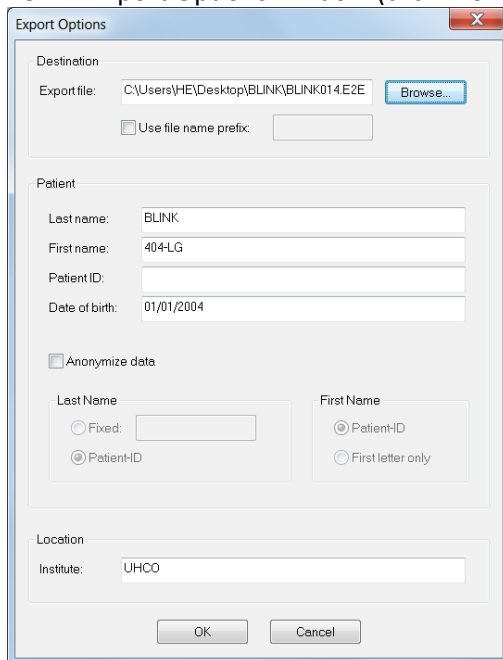
1. Select the OCT measurement from that day that had the best b-scan quality. Right-click and select “Export” and then “as E2E”.

Figure 18-13: Select the scan from that day that you want to export.



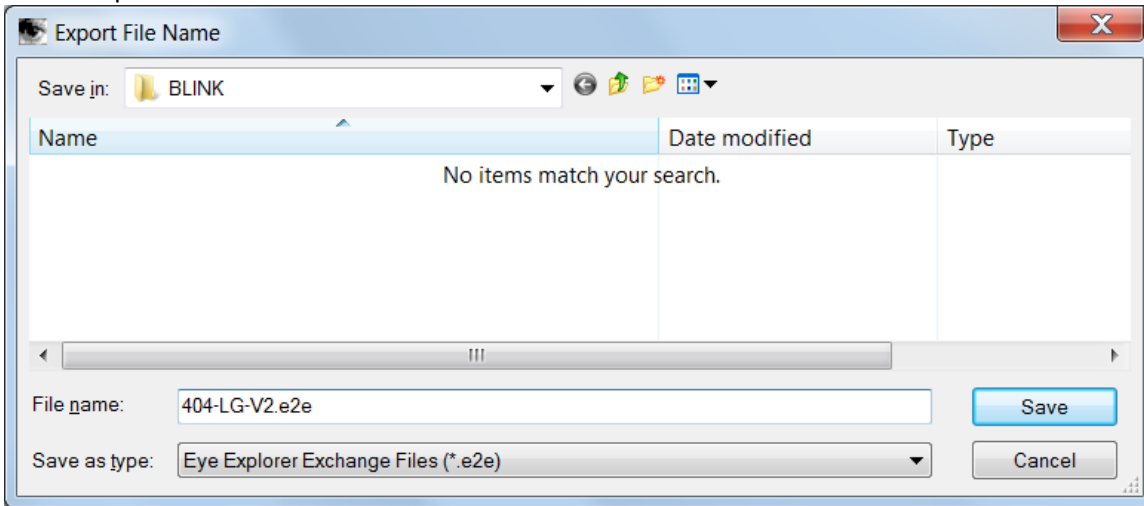
2. In the “Export Options” screen that appears, click the “Browse” button. (Do NOT click OK!) An “Export File Name” window will appear.

18-14: Export Options window (click Browse)



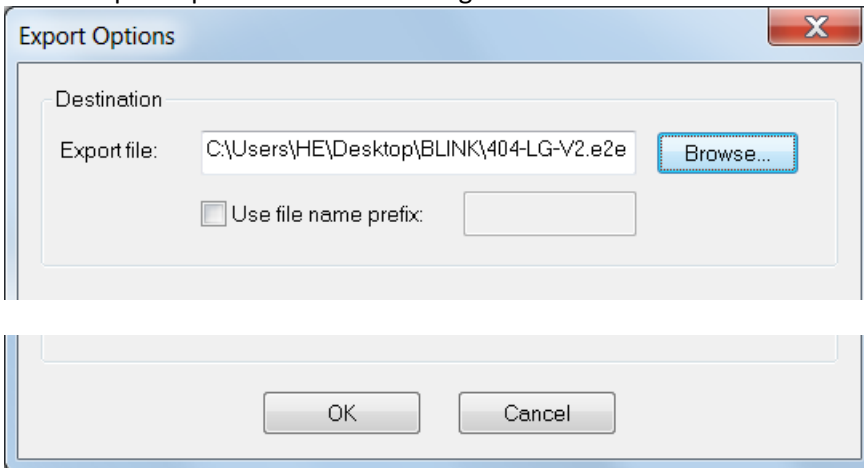
3. In the “Export File Name” window that appears, navigate to the folder where you want to save the exported file. In the “File name” field, name the file using the following file-naming scheme and click “Save”:
SubjectID-VX (where X is the visit number) - Ex: 404-LG-V2

18-15: 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.

18-16: 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 19: Central Autorefraction

Performed By

Cycloplegic: Masked Examiner at visits 1, 5, 7, and 9

Non-cycloplegic: Unmasked Examiner at visits 1 and 4 through 9

Eyes

OD and OS

Equipment

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

Introduction

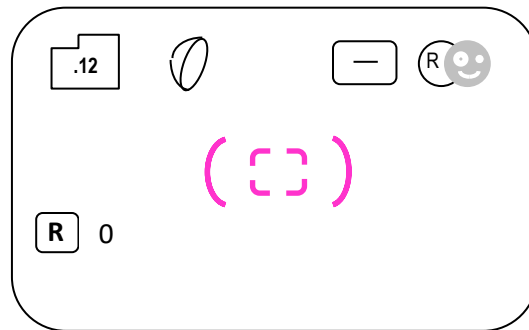
Cycloplegic central autorefraction is the primary outcome measure of the study. Ten valid measurements are performed on each eye. Dry (non-cycloplegic) autorefraction measurements will also be made at visit 1 (baseline) and every six months thereafter.

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 19-1 when set appropriately.

Figure 19-1: 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 DCC on the Calibration Form.

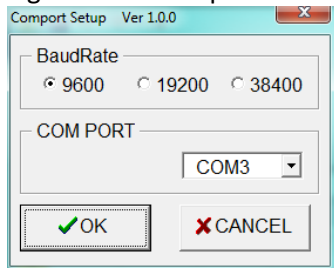
1. Place the model eye on the chin rest and ensure that the base of the model eye is parallel to the chin rest with the face of the model eye perpendicular to the measurement axis of the autorefractor.
2. Allow the autorefractor to warm up for 15 minutes.
3. Center the focused mires in the middle of 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 19-2.

Figure 19-2: 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:

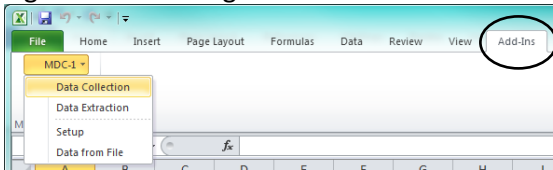
1. Instill one drop of 0.5% proparacaine or tetracaine in each eye.
2. Instill one drop of 1.0% tropicamide in each eye.
3. Wait five minutes.
4. Instill a second drop of 1.0% tropicamide in each eye.
5. Write the time of the second drop of tropicamide on a piece of paper.
6. Wait 25 minutes after the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

Measurement Procedure (Dry and Cycloplegic Autorefracton)

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

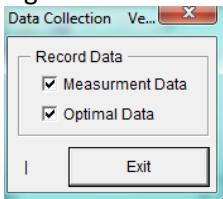
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated COM3).
2. Navigate to the central autorefracton Excel Template file (CentralAuto_Template.xlsx) located in the "BLINK Templates" folder on the desktop 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 the following window (Figure 19-4).

Figure 19-4: Successful connection between autorefracton 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 autorefracton measurements and make sure the subject's forehead is touching the forehead rest. The forehead rest should be removed for peripheral autorefracton.
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 19-5).

Figure 19-5: 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 20: Accommodative Lag with Manifest Refraction (Baseline Only)

Performed By

Unmasked Examiner

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.

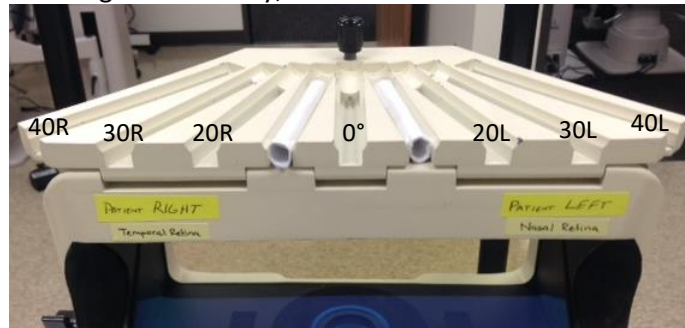
Accommodative lag with the manifest refraction in a trial frame is measured at Visit 1 (Baseline) only. The letter target used is 2.06 M in size (20/125 Snellen Equivalent). This letter size is used because it approximates text size in materials read by children in this age group.

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 by the unmasked examiner when measuring dry central autorefraction OD and OS earlier in the baseline (Visit 1) examination.

Measurement Procedure

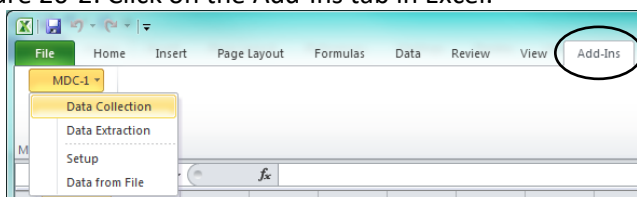
These measurements are performed by an unmasked examiner on the right eye only with normal accommodation (i.e., NO cycloplegia). A picture of the autorefraction horizontal target holder tray (examiner side) is shown in Figure 20-1.

Figure 20-1: autorefraction horizontal target holder tray, viewed from the examiner's side.



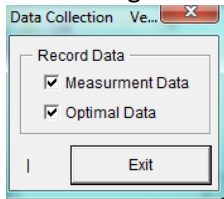
1. The Grand Seiko should still be connected to the laptop from having performed dry central autorefraction OU earlier during Visit 1. Confirm that the computer is still connected to the autorefractor.
2. If necessary, reconnect the MDC-1 software from within the "Add-Ins" tab in the Microsoft Excel ribbon (Figure 20-2) by clicking "MDC-1" and selecting "Data Collection" as described in the *Central Autorefraction* chapter.

Figure 20-2: Click on the Add-Ins tab in Excel.



- When the Grand Seiko is successfully connected to the laptop, you will see the window in Figure 20-3.

Figure 20-3: Signifies successful connection to laptop.



- 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.
- 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.
- Place the 33cm near rod in the central slot to measure accommodative lag in primary gaze only.
- 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.
- 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 20-4).

Figure 20-4: View in autorefractor that shows proper alignment.



- 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!)
- Obtain at least five readings without the "retry" message. When in doubt, take additional measurements to ensure that at least 5 measurements exist.
- Press Print and tape the printout in the location indicated on the exam form.
- When finished measuring, click the "Exit" button on the laptop to end the connection between the Grand Seiko and laptop.
- 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
- Upload the data file to subject's record using REDCap.

Chapter 21: Axial and Peripheral Eye Length

Performed By

Masked Examiner

Eyes

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

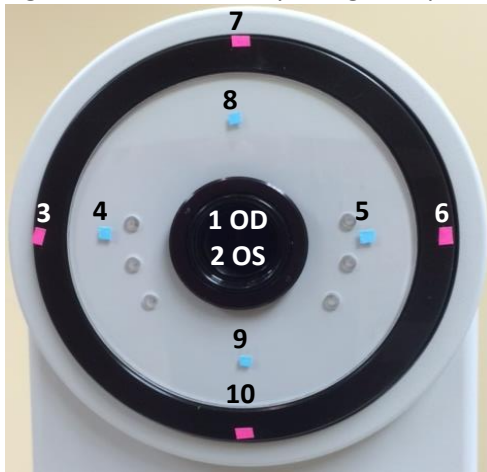
Equipment

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, 20° left, 20° right, and 30° right, 30° up, 20° up, 20° down, and 30° down – in that order (Figure 21-1). The targets at 30° are located 37.5 mm from the center of the aperture, and the targets at 20° are located 25.0 mm from the center of the aperture.

Figure 21-1: 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.

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 21=21 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-3-20L | 1/1/2004 |
| BLINK | 024-JT-4-20R | 1/1/2004 |
| BLINK | 024-JT-5-30R | 1/1/2004 |
| BLINK | 024-JT-6-30U | 1/1/2004 |
| BLINK | 024-JT-7-20U | 1/1/2004 |
| BLINK | 024-JT-8-20D | 1/1/2004 |
| BLINK | 024-JT-9-30D | 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.

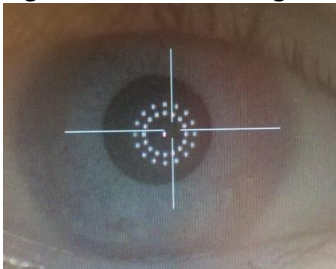
3. Press the Biometry icon on the left side of the screen.

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 21-2).

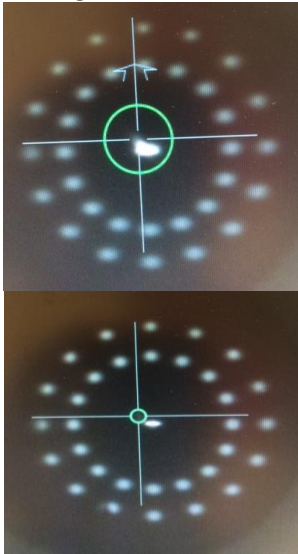
Figure 21-2: The unmagnified view of the eye. Focus the circles of dots, and place the blinking light in the crosshairs.





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 21-3).

Figure 21-3: 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.
- * Any reading on the Lenstar that is highlighted in red is not valid. Readings highlighted in red must be deleted and, if possible, replaced with a valid reading. If it is not possible to obtain five valid readings for a measurement location, a protocol deviation form should be completed, documenting that readings highlighted in red were deleted and could not be replaced with valid ones.

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 and open EyeSuite.
2. Click on **Tools**, then **Reporter**.
3. In the **Template File:** box, enter C:\Users\LenStar\Documents\Templates\CSV_BLINK.txt and click **Next**
4. In **Report File:**, 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
5. Click Next. The Lenstar will give you a prompt that the report was generated successfully.
6. Click Exit
7. In REDCap under Applications, select File Repository.
8. 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 22: Peripheral Refractive Error Without Contact Lens

Performed By

Masked Examiner

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 $\pm 20^\circ$, $\pm 30^\circ$, and $\pm 40^\circ$ from the line of sight. (Note: No measurements will be made at $\pm 10^\circ$, and these slots should be filled to prevent accidental placement of a target in these locations). Measurements in the vertical meridian will be made at $\pm 20^\circ$ and $\pm 30^\circ$ from the line of sight.

Autorefractor Setup

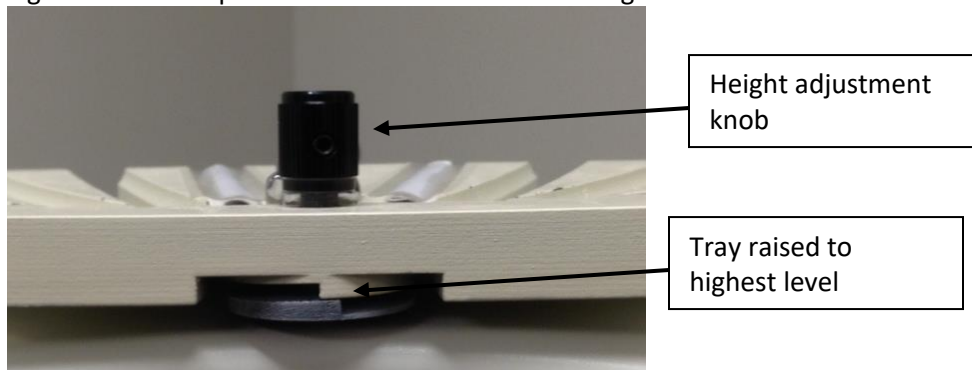
Distance from wall

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 22-1).

Figure 22-1: Set-up for horizontal meridian laser targets.



Placement of Targets for Vertical Measurements

Because physical targets on the wall are used for the peripheral vertical meridian measurements, the autorefractor must be at a fixed table height during vertical measurements so that the targets are at the correct peripheral eccentricity. With the laser pointer in the central (0°) location on the target holder tray, an 'X' should be placed on the

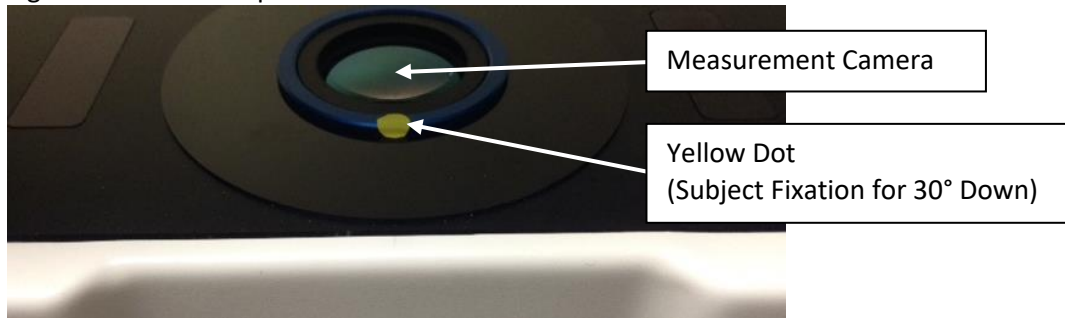
wall at the central (0°) location where the laser target falls to allow for quick verification that the table is at the correct height before beginning vertical measurements.

Up and Down refer to where the subject looks. Because the instrument housing obscures vertical views, subjects view vertical LED targets on the wall by looking into mirrors attached to the instrument housing; therefore, when subjects look UP during measurements, they see targets in the mirror that are physically inferior on the wall from the 'X'. When subjects look DOWN during measurements, they see a target in the mirror that is physically superior on the wall from the 'X'. Because of the location of the Measurement Camera on the autorefractor, a mirror cannot be placed on the instrument housing for the 30 Down measurement; therefore, the subject looks in the middle of a yellow dot located at the edge of the Measurement Camera closest to the subject for this measurement (Figure 22-2).

Targets should be placed on the wall in the following locations:

| Subject Gaze | Physical location of target |
|--------------|---|
| 30° UP | LED center 30.2 inches (76.8 cm) down from central 'X' |
| 20° UP | LED center 17.6 inches (44.8 cm) down from central 'X' |
| 20° DOWN | LED center 17.6 inches (44.8 cm) up from central 'X' |
| 30° DOWN | Center of yellow dot at edge of Measurement Camera closest to the subject |

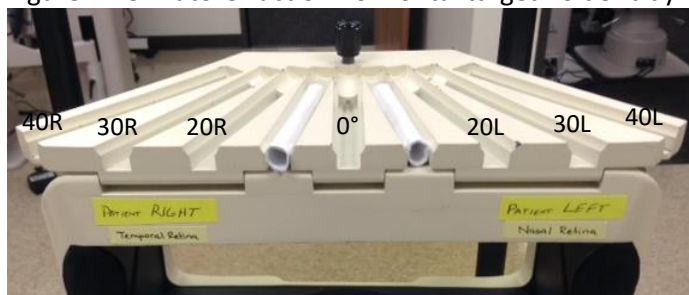
Figure 22-2: Fixation point for 30° down measurement.



Measurement Procedure (Horizontal Meridian)

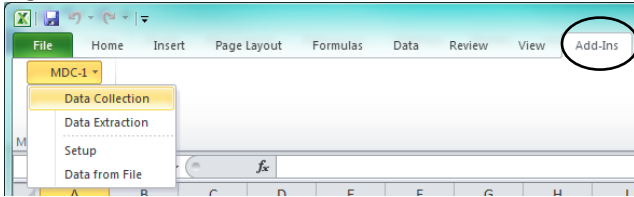
These measurements are performed by a masked examiner on the right eye only under cycloplegia. Left and right refer to the direction the subject looks. A picture of the autorefraction horizontal target holder tray, seen from the examiner's side (Figure 22-3).

Figure 22-3: Autorefraction horizontal target holder tray.



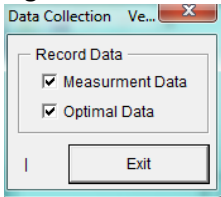
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated as COM3).
2. Navigate to the peripheral autorefraction Excel Template file (PeripheralAuto_Template.xlsx) located in the "BLINK Templates" folder on the desktop and open the file.
3. Once Excel opens the template, click the "Add-Ins" tab (Figure 22-4) in the ribbon and click "MDC-1" and select "Data Collection".

Figure 22-4: Add-Ins tab in Excel



4. Once the Grand Seiko successfully connects to the laptop, you will see the following window (Figure 22-5).

Figure 22-5: 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 40° 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.

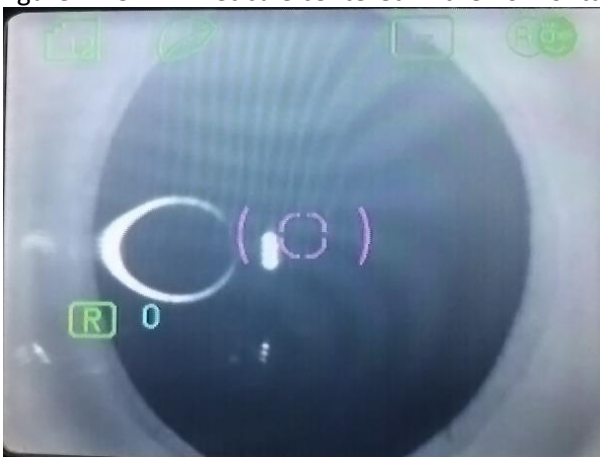
9. Obtain a view of the eye on the screen. For peripheral measurements, find the best iris focus by moving the instrument in or out. *Note: For peripheral measurements, the iris is used to focus (not the white keratometry circle).*

- 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 22-5).*

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

Figure 22-5: Pink reticule centered in the horizontal and vertical meridians of the pupil.

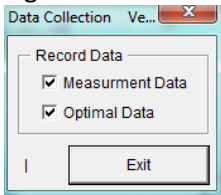


11. Obtain at least five “good” readings in which neither the sphere nor cylinder differ from the median by more than 1.00 D. When in doubt, take additional measurements to ensure that at least 5 “good” measurements exist.
12. Press Print and tape the printout in the location indicated on the exam form.
(Important: Remember to press the print button between each change in gaze!)
13. Repeat steps 8 through 12 with the laser pointer at 40° Left (40L), 30° Left (30L), 20° Left (20L), Central (0°), 20° Right (20R), 30° Right (30R), and 40° Right (40R).
(Note: It is important that you always follow this order – 40L, 30L, 20L, Central, 20R, 30R, 40R. 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.

Measurement Procedure (Vertical Meridian)

1. Verify that the table height is in the appropriate location by placing the laser pointer in the central (0°) holder. The laser spot should be at the height of the ‘X’ on the wall. If not, adjust the table height to match the location of the ‘X’ on the wall before proceeding.
2. 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).
3. Navigate to the peripheral autorefractor Excel Template file (PeripheralAuto_Template.xlsx) located in the “BLINK Templates” folder on the desktop and open the file.
4. Once Excel opens the template, click the “Add-Ins” tab in the ribbon and click “MDC-1” and select “Data Collection”.
5. Once the Grand Seiko successfully connects to the laptop, you will see the following window (Figure 22-6).

Figure 22-6: Window signifying successful connection to laptop.



6. Place an eye patch over the subject’s left eye.
7. Place the subject’s chin on the chinrest. The forehead rest may be used for these measurements to aid in patient positioning. It may be necessary to have assistance holding the subject’s head in place during measurements.
8. Turn on the 30° Up location LED target (which is actually 30° down on the wall because the subject views the target by looking into the superior mirror).
9. Have the subject turn his/her eye in the direction being measured to look into the mirror on the autorefractor and locate the LED target.
 - *Exception:* For 30° Down, the subject looks down in the middle of the yellow dot just below the Measurement Camera on the autorefractor.
10. Obtain a view of the eye on the screen and find the best iris focus by moving the instrument in or out.
11. Center the pink reticule in the vertical meridian and horizontal meridian of the pupil. *Note: do not center the pink reticule in the center of the white keratometry circle reflecting off the cornea!* An example showing correct vertical centration is below (Figure 22-7).

Figure 22-7: Pink reticule centered in the horizontal and vertical meridians of the pupil.



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.
14. Turn off the LED target (Only one target is illuminated at a time to avoid subject confusion and to improve fixation).
15. Repeat steps 9 through 14 for 20° subject looking Up (20U), 20° subject looking Down (20D), and 30° subject looking Down (30D). Turn on the appropriate target for the next location to be measured.

Reminders:

- The physical target location is opposite from the direction of the subject’s gaze – targets for subject Up gaze are down on the wall and targets for subject Down gaze are up on the wall)
- There is not a wall target for the 30° Down location; the subject looks in the middle of the yellow dot just below the autorefractor Measurement Camera. Ensure the subject is looking straight down and does not appear to be looking down and left or down and right.
- In down gaze, it may be necessary to lift the subject’s eyelid to get a good view during measurements.
- *It is important that you always follow this order – 30U, 20U, 20D, 30D. If you ever accidentally go in a different order, this must be noted in the Excel file once measurements are complete.*

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

Chapter 23: Aberrometry

Performed By

Unmasked Examiner

Equipment

At the Ohio State University site, a Complete Ophthalmic Analysis System for Vision Research (COAS-VR; AMO WaveFront Sciences, Pittsfield, MA) will be used to measure aberrations. At the University of Houston site, a Discovery System (Innovative Visual Systems, Elmhurst, IL) will be used to measure aberrations.

Introduction

Aberrometry of the right eye will be performed at Visit 5 to measure aberrations of the eye with no contact lens and again while wearing the study contact lens. The aberrations information will be used to evaluate the changes in higher-order aberrations caused by the study lens and image quality with the contact lens.

The left eye will be patched while measuring the right eye. All measurements will be made along the line of site under cycloplegic conditions. Refer to the appropriate procedures information based on your study site:

Ohio State University Site → COAS-VR

University of Houston Site → Discovery System

COAS-VR (Ohio State Site)

Calibration Verification

The COAS calibration should be verified throughout the study. The system calibrates each time the software is launched. To verify the calibration, place the COAS schematic eye on the chin rest. From the main COAS screen, click on Options > Configuration. Ensure the options are set to the following:

- Ref Plane tab – Reference Plane = Cornea
- Ref Plane tab – Seidel box should be checked
- Ref Plane tab – Chromatic Aberration Correction box should be checked
- The analysis diameter in the main COAS screen should be set to 6 mm.

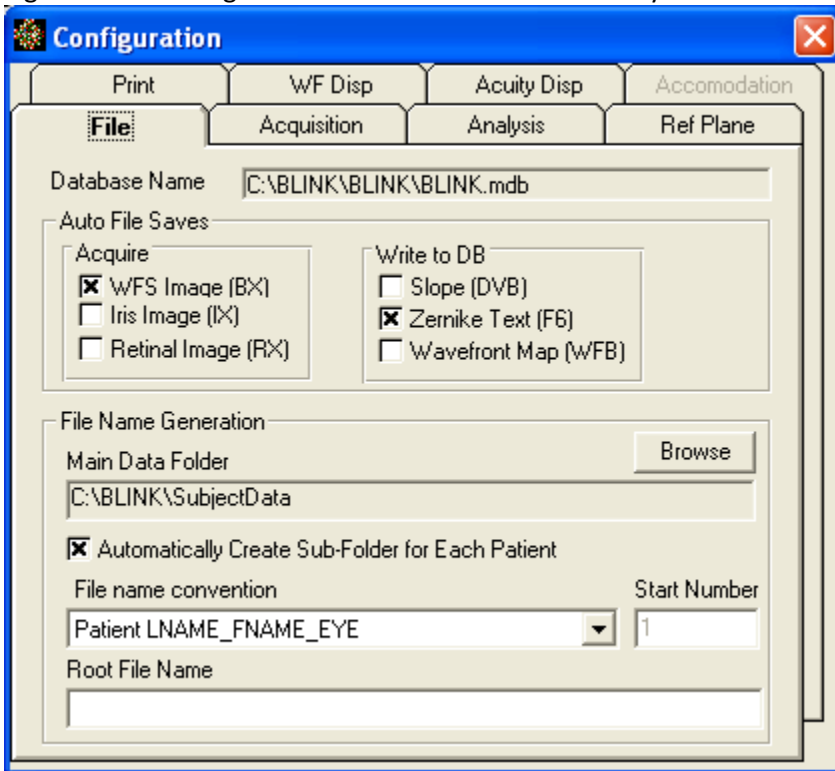
Important Note: After measuring the schematic eye, be sure to set the configuration values back to the settings described below in the configuration settings section of this chapter!

From the patient drop-down menu, select “testeye, testeye” as the subject. This subject name is to be used to verify the system calibration only. After aligning and focusing the image (see details below for focusing), acquire an image. Ensure that the readings obtained are within the tolerances for Sphere and Cylinder printed on the schematic eye. A total of three measurements should be made.

System Startup and Configuration Settings

1. Launch the COAS software after logging into Windows.
2. Turn on the two external LED switches on each side of the hot mirror.
3. From the menu bar, select Options > Configuration.
4. Once the configuration window opens, ensure that the following settings are marked in each of the tabs displayed in Figures 23-1 through 23-4.

Figure 23-1: Settings for COAS should be checked every time it is used.



File Tab:

- In the Acquire box, ensure the WFS Image (BX) box is checked. This box must be checked to save the raw data needed for analysis!
- In the Write to DB box, Zernike Text (F6) should be checked.
- The database name should be set to C:\BLINK\BLINK\BLINK.mdb
- The main data folder should be set to C:\BLINK\SubjectData
- File name convention should be set to "Patient LNAME_FNAME_EYE"

Note: If the database selected is not correct, exit the configuration screen and from the main COAS screen and use Database > Open to open the Database selection window. The BLINK.mdb file can be found at C:\BLINK\BLINK. After selecting the appropriate database file, press open.

Figure 23-2: Acquisition Type should be set to Single Acquire; SLD Power should be set to Normal.

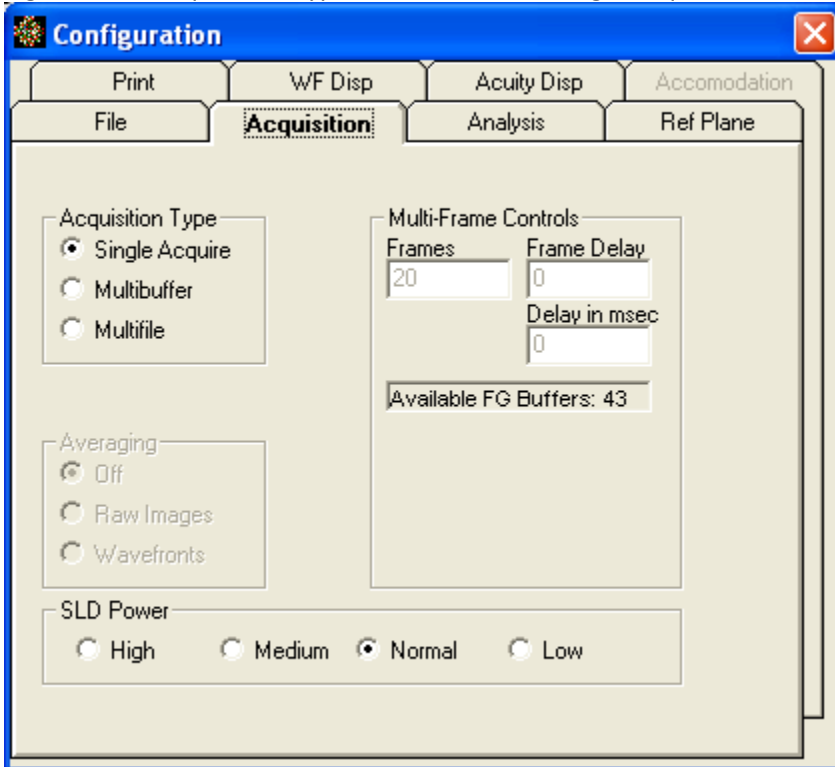


Figure 23-3: Zernike Order should be set to 6; WF Displayed Outside Zernike Analysis Pupil box and the Interpolate Data boxes should be checked; Zernike Format should be set to OSA Polynomials.

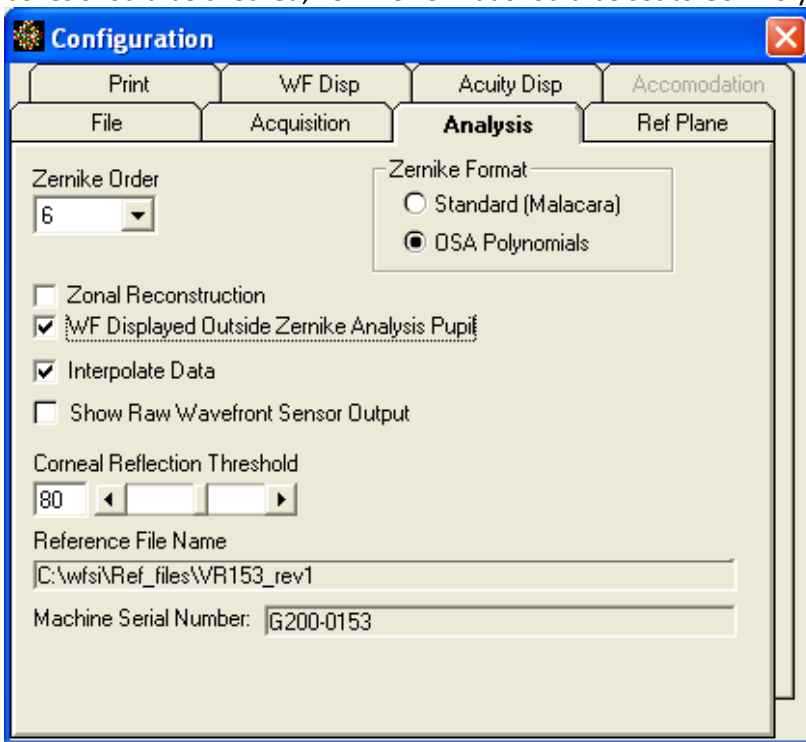
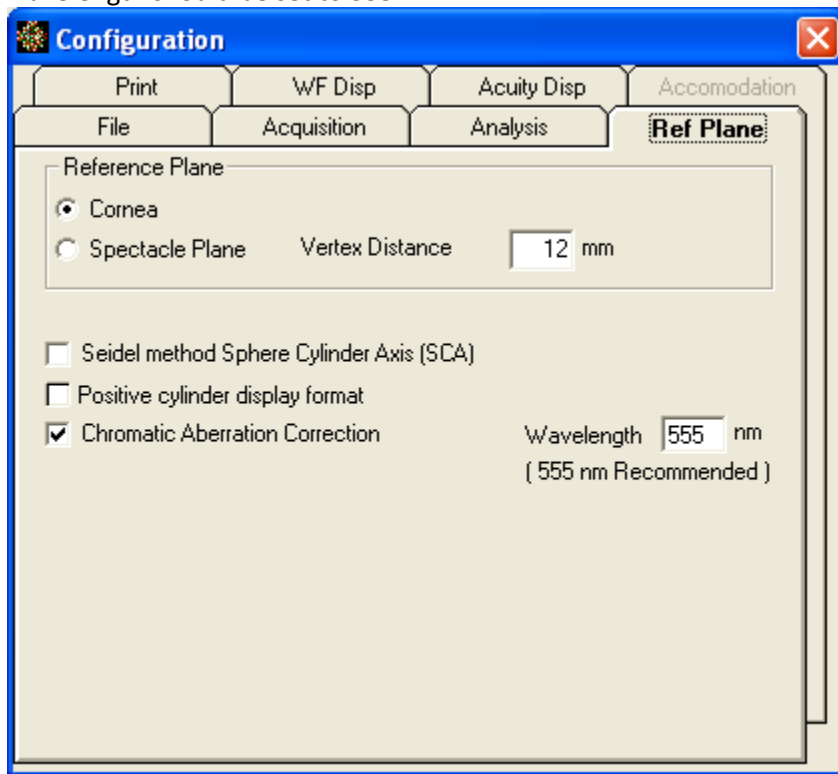


Figure 23-4: The Reference Plane should be set to Cornea; Chromatic Aberration Correction box should be checked; wavelength should be set to 555.



Note: After all configuration settings are verified, click the Red "X" in the upper right hand corner to close the Configuration box. (There is NOT an OK button that must be clicked.)

Add a Patient

Use the following steps to add a subject to the BLINK database. You will complete the procedure below twice for each subject. The first time, you will create a patient profile to use when measuring the eye without a contact lens (NoLens). The second time, you will create a patient profile to use when measuring the eye while wearing the study contact lens (WithCL). Complete the steps below to create each of these profiles.

1. Select Database > Add Patient.
2. In the First Name field, enter "NoLens" for one profile and "WithCL" for the other eye.
3. In the Last Name field, enter "BLINK-XXX-XX" where XXX-XX is the subject ID. For example: BLINK-204-TJ
4. For the Birth Date, only use the subject's year of birth. Use January 1 for the month and day. For a child born in 2007, enter 01/01/2007.

Note: The Patient ID number will automatically populate after you have entered the information above.

5. Press OK

Examples of how to enter the NoLens and WithCL profiles for a subject are shown in Figure 23-5.

Figure 23-5a: Profile without CL. Figure 23-5b: Profile with CL.

Add Patient

Patient ID:

First Name: MI:

Last Name:

Birth Date:

Monday, January 01, 2007 (7)

Clear OK Cancel

Add Patient

Patient ID:

First Name: MI:

Last Name:

Birth Date:

Monday, January 01, 2007 (7)

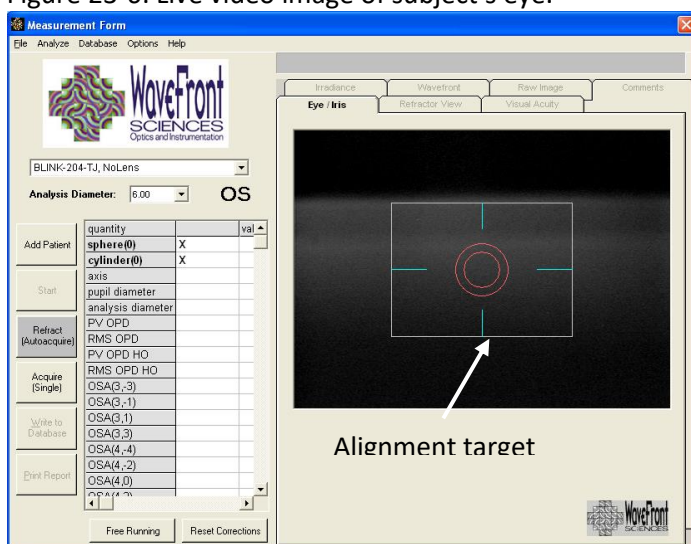
Clear OK Cancel

Measurement Procedure

The room lights should be off during measurements. The steps below will be used to measure the right eye with no lens, and again with the study contact lens. Measurements are made with cycloplegia.

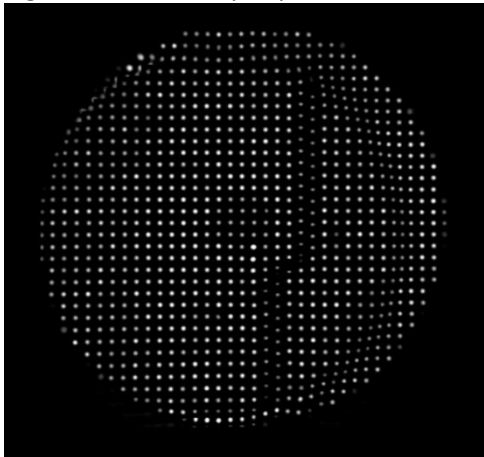
1. Patch the left eye. If testing with a contact lens, instill a drop of artificial tears.
2. From the drop down menu under the WaveFront Sciences logo on the screen, scroll until you find the subject's ID followed by the appropriate testing condition (i.e., NoLens or WithCL). For example: "BLINK-204-TJ, NoLens" would be selected for subject 204-TJ when measuring the right eye without a contact lens. Ensure that you have selected the correct testing condition each time before capturing wavefront images.
3. After selecting the appropriate ID and testing condition, use the sliding power control on the left side of the screen to enter the child's approximate OD spherical equivalent refractive error.
4. Have the child place his/her chin in the chinrest and press their forehead all the way forward.
5. Have the child look in the center of the COAS target which they will be able to see once they are correctly aligned and the room lights are turned off. An "Inter Wheel Target" intensity rheostat is located on the COAS. If glare is noted on the capture screen, decrease the target rheostat slightly.
6. Press the Start button on the screen to bring up the live video image of the subject's eye (Figure 23-6).

Figure 23-6: Live video image of subject's eye.



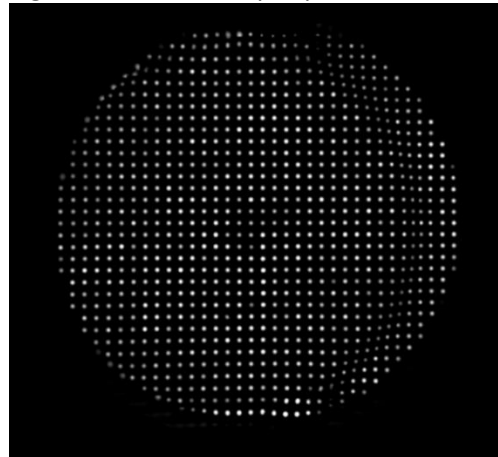
7. Use the control knobs on the instrument table and headrest to align the child so that the pupil is centered in the alignment target on the computer screen. The LED reflections on each side of the cornea should be aligned with the horizontal marking on the alignment target on each side of the red circles. (Hint: Be sure the child's teeth are together during alignment.)
 8. Focus the LED light(s) so that they are in focus on the computer screen by moving the subject closer to or farther away from the COAS using the appropriate adjustment knob on the headrest.
 9. Tell the subject to keep their teeth together and to "blink, blink and open wide." Press the large Green acquisition button on the COAS to start the measurement.
 10. After the measurement is complete, go to the "Raw Image" tab and view the spot pattern (Figure 23-6 a and b).
 - a. Verify that the child did not blink during acquisition
 - b. Verify that the pupil was centered and the pupil edge was not clipped by the window edges due to misalignment of the eye
 - c. Verify that the spot pattern does not contain distortions due to dryness. (Artificial tears can be instilled if there are issues with dryness-related distortions)
- Note:* If a blink, partially closed eye, clipped iris image, or spot distortions are found, click Start and repeat the measurement.)
11. If the raw image is good with no distortions, click Write to Database.
 12. Click Print Report. When the "Patient Report" screen opens, click Print to print a hard copy of the report on the attached printer.
 13. Repeat steps 6-12 until you have saved (saved = pressing Write to Database) and printed a paper copy of the report from three good acquisitions.
 14. After a total of 3 acquisitions have been collected, repeat all steps for the next measurement condition. Note: It is critical that you select the appropriate testing condition (NoLens or WithCL) from the subject drop down menu before you begin a new testing condition!

Figure 23-6a: Bad spot pattern with distortion.



Try adding artificial tears and repeat

Figure 23-6b: Good spot pattern without distortion.



Edge of CL optic zone can be seen on right side

Discovery System (University of Houston Site)

Calibration Verification

The Discovery System calibration should be verified throughout the study. To verify the calibration, clamp the test piece holder to a vertical post on the headrest assembly and insert the white Discovery test piece. Ensure that the test piece is aligned with the instrument axis (i.e., not tilted).

Click Patients > Select Patient. In the “Select Patient” window that appears, select “testeye, wavefront (white)” as the patient. This name is to be used to verify the system calibration only. After aligning and focusing the image (see details below for focusing), acquire an image. A total of three measurements should be made.

Add a Patient

Use the following steps to add a subject to the BLINK database. You will complete the procedure below twice for each subject. The first time, you will create a patient profile to use when measuring the eye without a contact lens (NoLens). The second time, you will create a patient profile to use when measuring the eye while wearing the study contact lens (WithCL). Complete the steps below to create each of these profiles.

1. Select Patients > Add Patient.
2. In the First Name field, enter “NoLens” for one profile and “WithCL” for the other eye.
3. In the Last Name field, enter “BLINK-XXX-XX” where XXX-XX is the subject ID. For example: BLINK-204-TJ
4. For the Date of birth field, only use the subject’s year of birth. Use January 1 for the month and day. For a child born in 2007, enter 01/01/2007.
5. Click Male or Female
6. Enter the “Patient number” using the subject ID followed by NoLens or WithCL separated by a hyphen. For example: 204-TJ-NoLens or 204-TJ-WithCL (Figures 23-7 a and b).
7. Press OK

Figure 23-7a: Profile without CL.

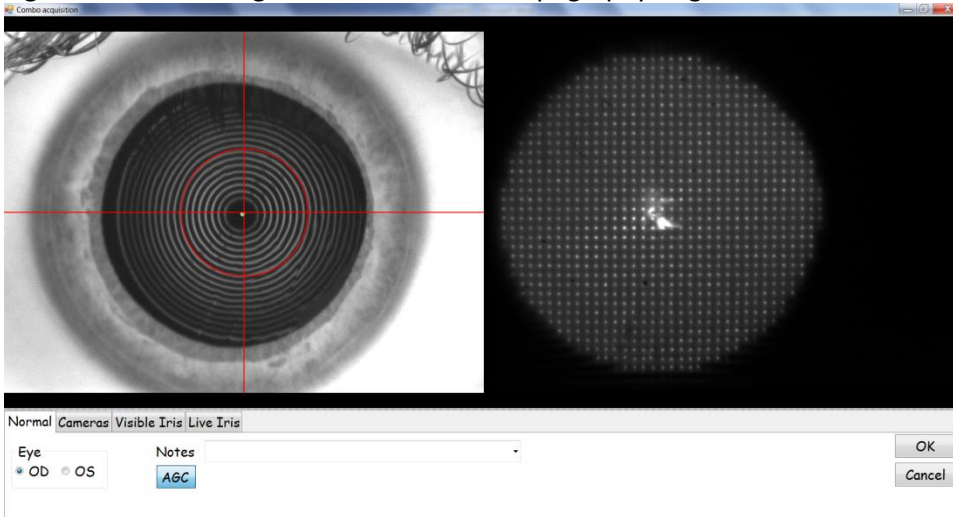
Figure 23-7b: Profile with CL.

Measurement Procedure

The room lights should be off during measurements. The steps below will be used to measure the right eye with no lens, and again with the study contact lens. Measurements are made with cycloplegia.

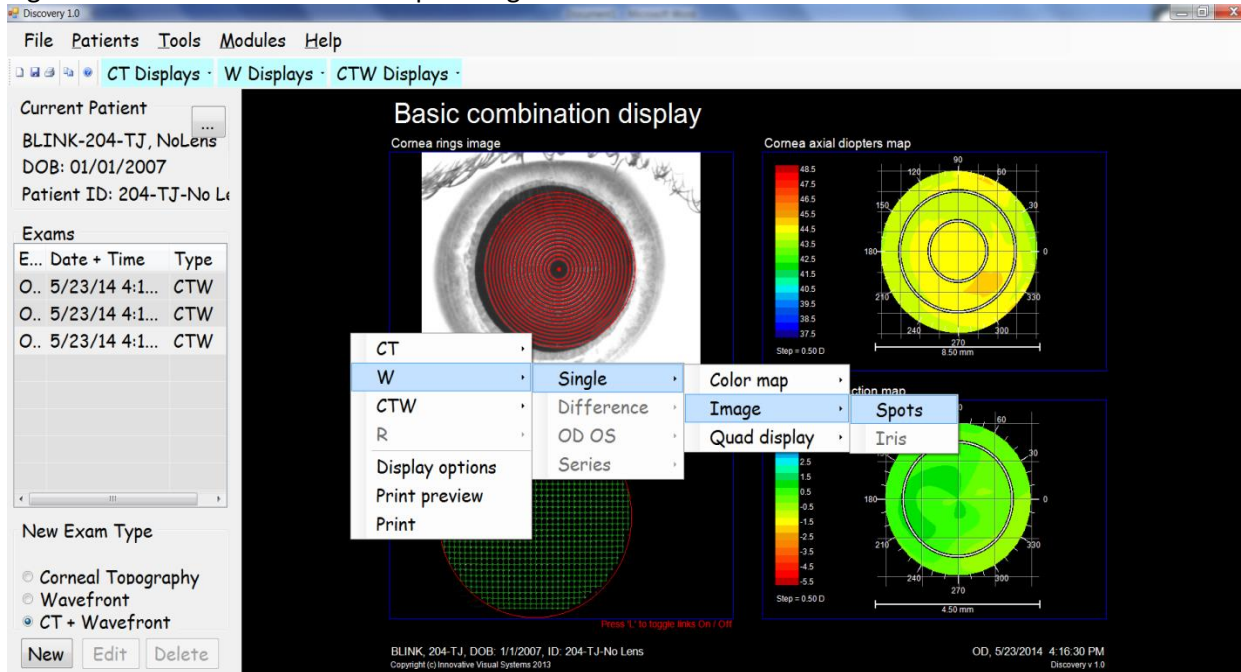
1. Patch the left eye. If testing with a contact lens, instill a drop of artificial tears.
2. Click Patients > Select patient. In the “Select Patient” window that appears, find the subject’s ID followed by the appropriate testing condition (i.e., NoLens or WithCL). For example: “BLINK-204-TJ, NoLens” would be selected for subject 204-TJ when measuring the right eye without a contact lens. Ensure that you have selected the correct testing condition each time before capturing wavefront images.
3. After selecting the appropriate ID and testing condition, click CT + Wavefront in the “New Exam Type” section and click New.
4. Have the child place his/her chin in the chinrest and press their forehead all the way forward.
5. Have the child look at the red light inside the instrument.
6. Use the joystick to align the child’s eye so that red crosshair is centered over the spot in the center of the pupil and move in and out to focus the topography rings (Figure 23-8).

Figure 23-8: Good alignment with focused topography rings.



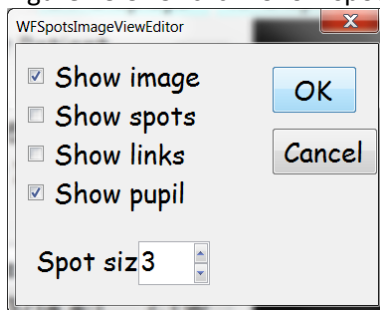
7. Press the joystick button to start the acquisition. “Acquisition start” will display on the upper left side of the screen and the crosshair will turn yellow.
8. Tell the subject to keep their teeth together and to “blink, blink, and open wide.”
9. While keeping the crosshair centered on the spot in the center of the pupil and maintaining focus, press the joystick button again to capture the wavefront.
10. After the measurement is complete, right click in the output window and select W > Single > Image > Spots to view the “Wavefront Spots image” screen so you can view the spot pattern.

Figure 23-8: How to examine the spot image.



11. On the “Wavefront spots image” screen, right click and select Display options. In the “WFSpotsImageViewEditor” window that appears, UNCHECK the “Show spots” and the “Show links” boxes and click OK (Note: Steps 10 and 11 only have to be done after the first acquisition after first launching the software. The software will remember these setting for future measurements unless the Discovery software is closed.)

Figure 23-9: Unclick “Show spots” and “Show links.”

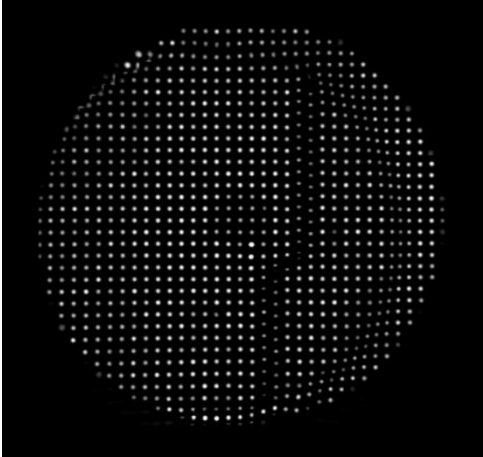


12. View the spot pattern to check for the following (Figure 23-10).
 - a. Verify that the child did not blink during acquisition
 - b. Verify that the pupil was centered and the pupil edge was not clipped by the window edges due to misalignment of the eye
 - c. Verify that the spot pattern does not contain distortions due to dryness. (Artificial tears can be instilled if there are issues with dryness-related distortions)

Note: If a blink, partially closed eye, clipped iris image, or spot distortions are found, click New and repeat the measurement.)

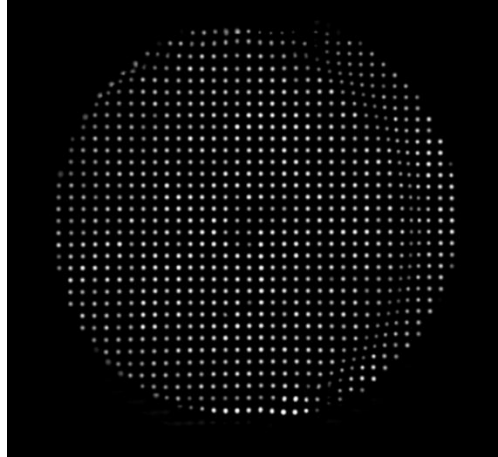
13. If the wavefront spots image is good with no distortions, repeat steps 4-12 until you have obtained three good images.
14. After a total of 3 good acquisitions have been made, repeat all steps for the next measurement condition. Note: It is critical that you select the appropriate testing condition (NoLens or WithCL) from the “Select Patient” list before you begin a new testing condition!

Figure 23-10a: Bad spot pattern with distortion.



Try adding artificial tears and repeat

Figure 23-10b: Good spot pattern without distortion.



Edge of CL optic zone can be seen on right side

Chapter 24: Peripheral Defocus With Contact Lens at Distance

Performed By

Unmasked Examiner

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

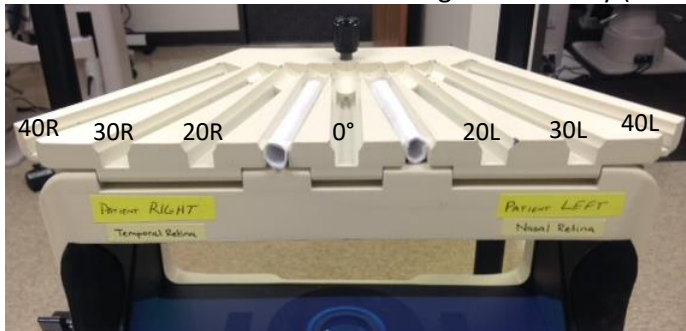
Peripheral defocus with the subject wearing their study contact lens measures the optical defocus that the peripheral retina receives while wearing the contact lens. Measurements are made at Visit 1 (Baseline) and at Visits 5, 7, and 9. All Grand Seiko settings and laptop computer settings are the same 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 ±20°, ±30°, and ±40° from the line of sight. No measurements will be made at ±10°, and these slots should be filled to prevent accidentally placing a target in these locations.

Measurement Procedure (Horizontal Meridian)

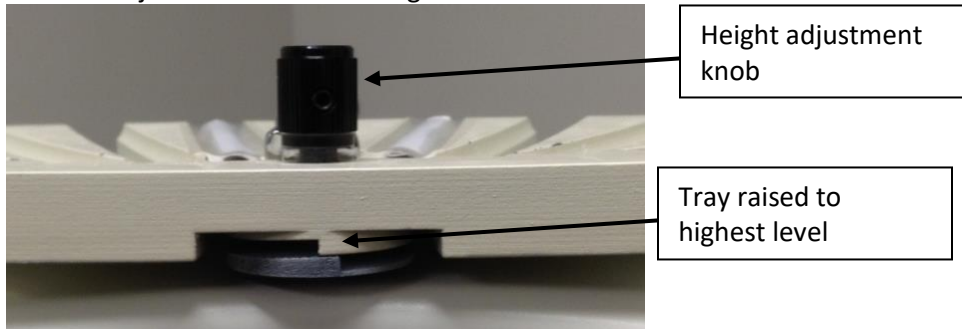
Left and right refer to the direction the subject looks. Figure 24-1 shows the autorefractor horizontal target holder tray (examiner side).

Figure 24-1: Autorefractor horizontal target holder tray (examiner side).



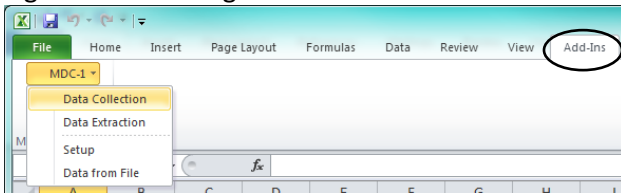
Before beginning, verify that the height adjustment knob on the subject side of target holder tray is rotated so that the back of the tray is at its highest level (Figure 24-2).

Figure 24-2: Adjustment knob at its highest level.



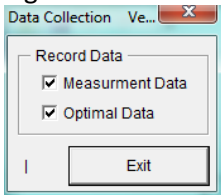
1. Attach the study laptop to the Grand Seiko using the USB cable (NOTE: The USB cable must be inserted into the USB port on the laptop that is designated as COM3).
2. Navigate to the peripheral autorefraction Excel Template file (PeripheralAuto_Template.xlsx) located in the “BLINK Templates” folder 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 24-3).

Figure 24-3: Adding the MDC-1 Add-In.



4. Once the Grand Seiko successfully connects to the laptop, you will see Figure 24-4.

Figure 24-4: Successful connection between autorefractor and laptop.

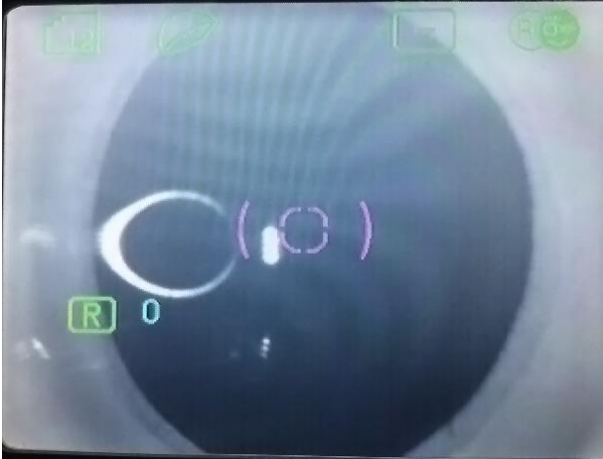


5. Place an eye patch over the subject’s left eye.
6. Place the subject’s chin on the chinrest. The forehead rest is not used for horizontal measurements because it prevents accurate instrument focusing during measurements. It may be necessary to have assistance holding the subject’s head in place during measurements.
7. Turn on the laser pointer and place it in the appropriate slot to measure with the subject looking 40° 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 24-5).*

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

Figure 24-5: 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 30° Left (30L), 20° Left (20L), Central (0°), 20° Right (20R), 30° Right (30R), and 40° Right (40R).

(Note: It is important that you always follow this order – 40L, 30L, 20L, Central, 20R, 30R, 40R. 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 25: Survey Administration

Performed By

Unmasked Examiner

Surveys

The Contact Information and History Forms contain personal identifying information, so they should not be sent to the Data Coordinating Center. All other forms will be completed online by the appropriate person, at the Visits indicated in Table 25-1.

Table 25-1: Forms, when completed, by whom, and whether or not they are sent to the Data Coordinating Center.

| Forms | Completed by | Not sent to DCC | 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 |
| PREP2 | Subject | | | | X | X | X |
| CISS | Subject | | X | | X | 4 only | X |
| Parent Compliance | 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 Unmasked Examiner may read the survey to the subject. The subject's parent may not read the survey to the child.
4. The Unmasked 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 26: Contact Lens Insertion, Removal, and Care Instructions

Performed By

Unmasked Examiner or Clinic Coordinator or other approved person

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 27: Chair's Office

The Chair's Office is under the direction of Dr. Jeffrey Walline, located at the Ohio State University College of Optometry. The Chair's office will employ a 50% FTE Study Coordinator to help perform the activities of this office. The Chair's office is responsible for all study communications, including organizing and managing all committee meetings, training sessions, and conference calls. This office oversees all clinic sites, and works directly with the Data Coordinating Center.

A monthly calendar of events, reflecting all meetings, conference calls and site visits will be distributed. In addition, the Chair's office will maintain an updated on-line directory with names, addresses, phone numbers and functions of all personnel involved in the study. The Chair's Office also maintains the Manual of Procedures.

Study Communications

Regular conference calls will be scheduled for discussion of study issues as they surface throughout the study. Other verbal and face-to-face discussions will occur through other telephone calls from the Chair's office to personnel at participating clinics, through FIG meetings, and through Executive Committee meetings. The Data Coordinating Center is also located at the OSU College of Optometry, so communication between the Chair's office and the Data Coordinating Center will be frequent and convenient.

To facilitate efficient communication among study personnel, the Chair's office will develop and maintain an on-line directory of all study personnel and resource centers. The calendar of events will also be available on-line, listing all scheduled meetings and conference calls. Frequent email communications and telephone calls will be used to alert study personnel to new or changing information, and for routine communications among study personnel.

The Chair's office will maintain the Manual of Procedures, and will distribute revisions to that document to both clinic sites, as necessary. The Chair's office will also work with the computer and information technology support personnel at the OSU College of Optometry to make available the Manual of Procedures on-line. This site will be password protected, and will be updated to assure that the current Manual of Procedures is always available to all study personnel, as revisions are made. This will simplify the task of verifying that all printed copies of the Manual of Procedures are indeed current.

The Chair's office will be the primary contact with outside organizations and individuals seeking information about the study. The Chair's office will field questions from interested parties, and be responsible for responding to requests for information.

Subject Searches

The Chair's office will conduct all searches for subjects deemed missing by the clinic sites. After a late visit has occurred and the clinical site's search for the subject has failed, the Chair's office will be notified, and will initiate a search. This additional search will utilize subject locator services, which have been used effectively in other clinical studies.

Publications

The Executive Committee will serve as a publications committee, and all coordination and communication involving publications and presentations will be performed through the Chair's office. The Chair's office will monitor the development of all study-related publications, and will facilitate their publication through distribution of drafts of manuscripts to contributing authors, by organizing conference calls, by identification and discussion of ideas and issues to be developed, by coordinating writing efforts, and by managing final production and submission of manuscripts.

Chapter 28: Glasses and Contact Lenses

Glasses

All subjects are eligible to receive a free pair of spectacle frames and lenses one time per year, but not at study closeout. Subjects will receive a prescription for glasses at study closeout, but not 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, the subject pays \$50 for the pair of glasses. If a subject desires transitions lenses, clip-on sunglasses, or any other item that costs extra, the subject pays retail cost for the extra item(s).

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 28-1. 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 28-1: 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 unmasked 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 29: Electronic Data Capture

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 29-1).

Table 29-1 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 <i>Do not send!</i> | Parent/Guardian | X | | | Update | Update |
| History – paper <i>Do not send!</i> | Parent/Guardian | X | | | | Update |
| Myopia Risk Factor | Parent/Guardian | X | | | | |
| Baseline Examination | Unmasked examiner | X | | | | |
| Semiannual Examination | Unmasked examiner | | | | X | |
| Baseline Masked | Masked examiner | X | | | | |
| One Week Examination | Unmasked examiner | | X | | | |
| Three Week Examination | Unmasked examiner | | | X | | |
| Semiannual Examination | Unmasked examiner | | | | X | |
| Annual Examination | Unmasked examiner | | | | | X |
| Annual Masked | Masked examiner | | | | | X |
| Contact Lens | Subject | | | X | X | X |
| PREP2 | Subject | | | X | X | X |
| CISS | Subject | X | | X | 4 only | X |
| Parent Compliance | Parent/Guardian | | | X | X | X |
| Unscheduled Visit – as needed | Unmasked examiner | | | | | |
| Discontinuation – as needed | Unmasked examiner | | | | | |
| Adverse Event – as needed | Unmasked examiner | | | | | |
| Crossover – at time of crossover | Unmasked examiner | | | | | |
| Calibration – monthly | Clinic Coordinator | | | | | |

Forms Not Transmitted to DCC

The Contact Information Form, the History Form, and the Randomization Form should never be transmitted to the Data Coordinating Center 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 Chair's office 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

Both sites will purchase computers 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 DCC. 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 DCC, 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 PREP2, the Convergence Insufficiency Symptom 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.

A training session on the use of the REDCap system will be provided prior to any data entry. For those personnel employed at the outset of the study, the session will allow for users from both Ohio State and the University of Houston to receive training from the personnel in the CCTS. Personnel who join the study team at a later date will be trained by the clinic PI with the DCC available to assist.

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 Data Coordinating Center 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 Masked Examiner or by the Unmasked 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 Data Coordinating Center 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. The DCC will maintain a comprehensive record of all authorized personnel, with their role on the study, and the access privileges.

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. The University of Houston personnel will also receive OSU Medical Center access identification in order to facilitate their remote log-in. Issuance of an OSUMC id depends upon the completion of a LexisNexis background check. Different levels of user access are determined based upon the role of the user in the study. For example, a masked examiner will be restricted to access only that information that would not reveal the treatment group assignment. 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. Data access groups will also be created to prevent records from the University of Houston clinic site being accessed by a user from the Ohio State University clinic site and vice versa.

Chapter 30: Certification

Introduction

The purpose of certification requirements in the study is to assure that procedures are being performed uniformly and consistently in accordance with the protocol at each clinic site. Certification is supervised by the Executive Committee and its designates. Prior to examining subjects, the clinic PIs must be certified in all tasks except study coordination so that they can answer questions, and a masked examiner must be certified to perform the masked outcome measures. The following measures require certification:

- Visual acuity
- Modified Thorington
- Accommodative lag
- Pupil size
- Cycloplegic autorefraction
- Axial length
- Peripheral autorefraction
- Peripheral eye length
- Study coordination

In order to maximize stability of personnel and to enhance data quality, trainees at clinic sites (e.g., optometry students and residents) cannot be certified as study personnel, unless approved by the Study Chair. All study personnel are required to read the Manual of Procedures, and they must complete a written test and a telephone interview with the examiner who certifies the task. If a new person needs to be certified, the Clinic PI should notify the Study Chair. Each person certified in at least one measure will be assigned his or her certification initials by the Chair's office. These initials should be entered on all forms as indicated. Certification is maintained as long as the person performs the task on at least five subjects per year. If the person does not perform the task on at least five subjects per year, then the examiner must be re-certified. Those who can conduct the in-person certification include the Study Chair and the Clinic PIs. The DCC maintains the certification status of the clinic personnel, and notifies the clinic when renewal is necessary.

Certification for Visual Acuity

The Clinic PI and Unmasked Examiners at each clinic site must be certified to perform visual acuity. The certification requirements for visual acuity are:

- Read the Manual of Procedures, especially the chapter titled Visual Acuity.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person visual acuity certification session.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Certification for Modified Thorington

The Clinic PI at each site and Unmasked Examiners must be certified to perform Modified Thorington. The certification requirements for Modified Thorington are:

- Read the Manual of Procedures, especially the chapter titled Modified Thorington.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person Modified Thorington session.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Certification for Accommodative Lag

The Clinic PI at each site and Unmasked Examiners must be certified to perform accommodation measurement. The certification requirements for accommodative lag are:

- Read the Manual of Procedures, especially the chapter titled Accommodative Lag.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person accommodative lag session.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Certification for Cycloplegic Autorefraction

The Clinic PI at each site and Masked Examiners must be certified to perform cycloplegic autorefraction. The certification requirements for cycloplegic autorefraction are:

- Read the Manual of Procedures, especially the chapter titled Cycloplegic Autorefraction.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person cycloplegic autorefraction certification session.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Certification for Axial Length

The Clinic PI at each site and the Masked Examiners must be certified to perform Axial Length. The certification requirements for Axial Length are:

- Read the Manual of Procedures, especially the chapter titled Axial Length.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person axial length certification session.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Certification for Peripheral Autorefraction

The Clinic PI at each site, the Masked Examiners, and the Unmasked Examiners must be certified to perform peripheral autorefraction measurements appropriate for their role. The certification requirements for peripheral autorefraction are:

- Read the Manual of Procedures, especially the relevant chapters titled Peripheral Refractive Error Without Contact Lens, Peripheral Defocus With Contact Lens, and Peripheral Defocus With Contact Lens at Near.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person peripheral autorefraction session.

After satisfactory completion of requirements, verification of certification is given to clinic and DCC by Chair's Office.

Certification for Peripheral Eye Length

The Clinic PI at each site and the Masked Examiners must be certified to perform peripheral eye length. The certification requirements for peripheral eye length are:

- Read the Manual of Procedures, especially the chapter titled Peripheral Eye Length.
- Review the EDC Form.
- Complete the written certification examination.
- Complete an in-person peripheral eye length certification session.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Certification for Clinic Coordination

The Clinic Coordinator should be certified prior to study start-up at each clinic site. Certification will be granted upon successful completion of the certification.

The Clinic Coordinator's role is critical to the smooth day-to-day operation of the clinic site, but the tasks may be assigned to a less-than-full-time person. The training program will emphasize skills in subject management, data quality control, and organizational ability. Similarly, the certification procedure will evaluate simulated data with problems to evaluate data editing expertise and hypothetical subject problems to evaluate familiarity with the protocol and subject follow-up procedures.

The Clinic PI at each site and the Clinic Coordinator must be certified to clinic coordination, along with the Study Coordinator. The certification requirements for clinic coordination are:

- Read the Manual of Procedures.
- Complete the written certification examination.

After satisfactory completion of all requirements, verification of certification is given to the clinic and the DCC by the Chair's Office.

Chapter 31: Study Organization and Policy Matters

Executive Committee

The Executive Committee has overall responsibility for directing the activities and policies for the study, except for responsibilities specifically assigned to other committees. The Executive Committee meets in person at least twice each year and by telephone conference calls as needed. Additional meetings may be called by any member of the Executive Committee.

The following are permanent members of the Executive Committee:

- Study Chair
- Clinic PIs
- Data Coordinating Center Director

The Study Chair may appoint other individuals to the committee for one-year terms as necessary to assure the scientific quality of the deliberations. All members are expected to file statements with the Study Chair describing any personal or professional involvement with manufacturers or others who might benefit financially from the findings of the study.

Some of the specific functions of the Executive Committee are:

- to deal with day-to-day operational matters which do not involve changes in the study protocol or policy;
- to assign priorities for study activities;
- to perform administrative and logistic functions for the study, including scheduling meetings, scheduling site visits, etc.
- to implement changes suggested by the Data Safety Monitoring Committee

Publicity

All publicity and press releases for the study are to have prior approval of the Executive Committee. Study investigators who are approached by the press for information concerning the study should refer these inquiries to the Study Chair, who will consult with the Executive Committee.

It is recognized that when information is sought from an individual investigator by the local press in his or her own community, it is sometimes necessary or desirable for the investigator to handle the request. In such an event the participating investigator should speak as an individual and not as the official representative of the study group. This fact should be made clear to the press; however, the information given out should be accurate and should reflect the general policy and views of the group. The Study Chair should be informed of all local presentations to the press and be sent a copy of the material published.

Publications

The Executive Committee will review all written reports prepared for publication. All reports from the study will list the primary author, co-authors, and the Study Group as the last author. All professional participants of the study, including those at the Chair's Office and the Data Coordinating Center, will be listed at the end of each paper and are considered as authors or contributors. In major papers, all study personnel, past and present, will be listed with the approval of the Clinic PI for whom they have worked.

Conflicts regarding authorship are resolved by the Executive Committee. General guidelines for authorship are: active participation in the production of the manuscript or other important contribution. Authorship rights are not available for membership on the writing committee only, use of data only, or signing the copyright form. If the timeline for a paper has expired with no substantial evidence of progress, authorship rights are assumed to have expired. The DCC will contact the primary author, and leadership of the paper will be negotiated. The Executive Committee will be informed of changes in lead authorship. An individual may be given an acknowledgment for reading and providing critical comments on the manuscript. An investigator at the DCC will be added to the author list on all papers which require his or her statistical input.

The Executive Committee establishes writing committees for principal papers from among the investigators. Investigators may volunteer for writing assignments and suggest additional topics where appropriate. A representative

of the DCC will be appointed to writing committees on papers or presentations requiring study data. Investigators may volunteer for writing assignments and suggest additional topics where appropriate.

The investigator should submit an abstract and a short description of the proposed paper including co-authors, data to be reported and timeline for drafts and submission. This information should be sent to the Study Chair. The Executive Committee is responsible for reviewing the proposal's merit and deciding if it should be a study publication. This review process is intended to ensure the quality of study publications and to refine the proposal. The Executive Committee is responsible for determining priorities (timeline and order of preparation) of proposed papers/presentations. Upon approval of the proposed paper/presentations, a detailed analysis plan and timetable are developed with the DCC.

The DCC is responsible for maintaining a database that tracks proposed and approved study publications and presentations. A list of approved study publications and presentations will be distributed to all investigators on a regular basis. Interested investigators are invited to contact the primary author to add their name to the writing group.

Should the workload associated with the preparation of papers exceed the resources of the DCC, it will be the responsibility of the DCC in conjunction with the Executive Committee to establish priorities. It will be the responsibility of the DCC to contact primary authors when timelines are not met. Major problems in the preparation of manuscripts are referred to the Executive Committee.

The primary author is responsible for coordinating all activities related to the writing and submission of papers and abstracts. This includes arranging conference calls, discussing analytic plans with the DCC, assigning writing responsibilities to co-authors, maintaining timeliness, determining the order of authorship, circulating drafts to co-authors, and circulating final drafts to the Executive Committee. Upon circulation of the draft, there will be a two-week period during which members can make comments about the paper.

If the focus of the paper changes as it moves from abstract to the manuscript stage, the primary author will notify the Study Chair in writing. The Study Chair will be responsible for insuring that the revised proposal receives appropriate review.

Each publication must acknowledge support as follows: "NIH U10 EY023204, 023206, 023208, 023210, P30 EY007551, and UL1 TR001070."

The Study Chair will send a letter of approval with all manuscripts when they are submitted for publication. Some journals require that all individuals listed as member of the study group sign the copyright waiver form. If so, the writing committee will enlist the assistance of the Study Chair's Office to obtain these signatures.

Protocol for Submitting Publications

- Ideas for paper topics must be approved by the Executive Committee
- The Executive Committee will form a writing committee and determine a lead author
 - The lead author is typically the first author
 - Named authors include the writing committee members (generally 2 to 4, not including the Executive Committee) and the Executive Committee
- The writing committee, working with the Data Coordinating Center, should write Draft #1 of the paper.
- When all writing committee members are okay with Draft #1 of the paper, the paper should be submitted to the Study Chair
 - The Study Chair will add the Study Group listing to the manuscript and send the manuscript to the entire study group for review
 - The Study Chair and/or lead author will make edits to the manuscript
 - Responses must be received from *all* members of the Study Group
- Draft #2 will be sent to the DSMC for comments and approval
- Draft #3 will be submitted to the appropriate journal with the Study Chair as the corresponding author
- When reviews are received, the Study Chair and/or lead author will respond point-by-point to the reviews
- Draft #4 will be submitted to the journal, and this will continue until it is accepted or withdrawn
- When page proofs are received, the Study Chair, first author, and Data Coordinating Center Director will review the manuscript

Presentations

Oral presentations and abstracts to be printed must be approved in advance by the Executive Committee. No unpublished study results may be used for oral presentations, local or otherwise, unless a specific exception is granted by the Executive Committee. Study results include all data collected for the study. The above restrictions do not apply to local presentations of the design of the study, provided these presentations contain no unpublished study results. Such presentations are encouraged to stimulate subject recruitment.

Publications from Ancillary Studies

Manuscripts dealing with ancillary studies carried out in conjunction with the study must be sent to the Executive Committee for review before submission for publication. Investigators may not independently use study data collected at their clinic.

Ancillary Studies

Individual investigators who desire to carry out ancillary studies are encouraged to do so. Ancillary studies may greatly enhance the value of the study and ensure the continued interest of all investigators. However, to protect the integrity of the study, ancillary studies must be reviewed and approval by the Executive Committee before their inception, whether or not they require supplemental funds.

No additional tests or measures can be made on study subjects without prior approval by the Executive Committee and IRB approval. Data analysis, unless of special interest to one of the DCC investigators, is the responsibility of the ancillary study investigators.

Definition of an Ancillary Study

An ancillary study is a research project that requires either:

- 1) supplemental observations or procedures to be performed on any study subject according to a set protocol, or
- 2) additional work to be done by or information to be obtained from the DCC.

Site Visits

Site visits will be performed by Dr. Walline (Study Chair) along with either Dr. Jones-Jordan and/or the Study Coordinator to ensure quality control and to check on the operations of each clinic site. Each clinic site will be visited at least once during the recruitment phase of the study.

Site visits are necessary to assure that there is standardization of procedures, that the clinic site personnel have been adequately trained, that the clinic site facilities meet all standards, and that subjects and their data are being managed as specified in the protocol. The site visit team will also provide assistance to the clinic site in solving logistical problems by conveying efficient, accurate solutions used in another clinic site. A site visit will be performed at both clinic sites during each year.

The site visit should be scheduled so that the clinic site staff members may arrange their day appropriately, usually a month or more in advance. A copy of the site visit agenda is sent to the clinic site Principal Investigator. The Principal Investigator or Clinic Coordinator informs the site visit team of any local scheduling constraints. The site visitors re-arrange the agenda to meet the scheduling constraints of the clinic site.

The site visit team will prepare for the visit by reviewing recent performance reports, and comments solicited by the Study Chair and DCC. These materials are used to make a list of outstanding issues. Site visits will generally begin in the morning and require one day. Strict adherence to the protocol is stressed throughout the site visit.

General areas of review during the site visit are listed below:

- Clinic site staff, facilities, and equipment
- Up-to-date documentation, including the Manual of Procedures and protocol memoranda
- Storage and access to files, including proper storage of signed consent forms and handling of edit statements
- Flow of subjects through examinations
- Observation of unmasked and masked examiners during examinations
- Observation of the procedures to ensure protection of masking

- Observation of the procedures used by the Clinic Coordinator to make sure all data are complete and accurate
- Meeting with the Clinic PI to discuss recruitment and retention issues
- Meeting with all other study clinic site staff to discuss any relevant issues

Within two weeks of completion of a site visit, a written summary prepared by the site visit team will be sent in draft form to the Clinic PI and Clinic Coordinator who will review it for accuracy. The final version will be sent to the same individuals and also to the DCC. A copy is also maintained in the library of documentation in the Chair's Office.

Chapter 32: Adverse Events

Background

An important consideration in a clinical trial, particularly one that uses a contact lens treatment group, is the guidelines to be followed in case an adverse event occurs. The Unmasked Examiner should first determine whether an adverse event occurred, using information written in Determination of Adverse Events, then categorize the event according to the guidelines listed in Categorization of an Adverse Event. The Unmasked Examiner should report Serious and Unexpected events to the Clinic Coordinator and Clinic PI immediately. The Clinic PI and Clinic Coordinator are responsible for ensuring that Serious and Unexpected Adverse Events are appropriately reported as described in Categorization of an Adverse Event.

Determination of Adverse Events

There are three ways that an Adverse Event can be identified.

1. The subject experiences/presents with ocular signs or symptoms worse than those encountered during routine contact lens wear (e.g., a slit lamp sign of \geq Grade 3). It is up to the Unmasked Examiner to determine when an Adverse Event Form should be completed.
2. At every visit, the Unmasked 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?"

The Unmasked Examiner should document an adverse event in response to this question if:

1. the condition is chronic, not previously documented, and requires a change in medications or change in daily activities over an extended period, or
2. the examiner feels it is acute and warranted, such as a broken bone or head trauma (not warranted is cold, flu, or ear infection).

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 Unmasked Examiner, after asking appropriate follow-up questions.

For example, if a parent says that her child had a headache, the Unmasked Examiner should ask appropriate questions to determine the quality, frequency, onset, location, duration, associations, 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 Unmasked Examiner believes that it may be related to the study treatment, then an Adverse Event Form should be completed.

3. The Unmasked Examiner should ask the parent the precursor question about items in the Symptom Checklist at the beginning of each visit form after Baseline, "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 and/or child should answer "yes" or "no" to each symptom. If the answer is "yes," then appropriate follow-up questions should be asked so that the Unmasked Examiner can determine whether or not the symptom may be related to the study treatment and therefore an Adverse Event Form should be completed.

Final decision of whether or not each event is an Adverse Event will be decided by the Executive Committee during weekly conference calls. In general, if the Unmasked Examiner is unsure of whether or not something should be categorized as an adverse event, an Adverse Event form should be completed. When completing the Adverse Event Form, the Unmasked Examiner should **not** include information about the subject's treatment group assignment, so that the Executive Committee's decision of whether or not something is an Adverse Event is less likely to be potentially biased.

Categorization of an Adverse Event

The following sections help to categorize the adverse event. If the event is serious or unexpected, then special reporting is required. Otherwise, complete an Adverse Event Form and submit it to the Data Coordinating Center as soon as possible.

Type of Adverse Event

- **Ocular:** Pertaining to the eye and adnexa
- **Non-ocular:** All other events

Significance

- **Serious:** 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.
- **Non-serious:** all other events

Severity

- **Mild:** Events that lead to easily tolerated signs or symptoms that do not change normal activities or require treatment with prescription medications (may require over-the-counter medications)
- **Moderate:** Events that lead to signs or symptoms that may interfere with daily activities and/or are treated with prescription medication
- **Severe:** Events that are usually incapacitating or sight-threatening and generally require prescription medication

Would Contact Lens Wear Have Been Discontinued?

Regardless of whether the subject discontinues contact lens wear, the unmasked examiner should determine whether s/he would have discontinued contact lens wear in that situation. For example, a subject may have discontinued contact lens wear for two days while she had a fever. If the doctor determines s/he would not have recommended discontinuation contact lens wear, then the answer would be No.

- **No:** Doctor would not have discontinued contact lens wear
- **Yes, temporarily:** Doctor would have temporarily discontinued contact lens wear
- **Yes, permanently:** Doctor would have permanently discontinued contact lens wear

Was Event Unexpected?

• **Ocular:** An event is *expected* if it is on the list of potential complications from contact lens wear presented in the parental permission document OR is an occasional ocular finding in a pediatric population (eg, flashes, floaters, or atrophic retinal hole); otherwise, the event is unexpected. Expected events with contact lens wear include:

- Burning, stinging, and or itching of the eyes
- Less comfort after all day wear
- A feeling like there is something in the eye
- Inflammation of the cornea (clear window on the front of the eye) and/or scratch of the cornea
- Swelling of the cornea
- Small blood vessels growing into the cornea
- Small defects in the corneal surface (corneal staining)
- Redness
- Bumps on the inside of the eye lid (tarsal abnormalities)
- Inflammation of the inner eye (iritis)
- Excessive watering, unusual eye secretions, or redness of the eye
- Blurred vision
- Rainbows or halos around objects
- Sensitivity to light

- Dry Eyes
- **Non-Ocular:** An event is *unexpected* if it meets *all* of the following criteria:
 1. unexpected (in terms of nature, severity, or frequency) given the research protocol, informed consent document, and subject population
 2. related or possibly related to participation in the research
 3. suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized

Related or Unrelated

- **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.

Prompt Submission of an Adverse Event to the IRB

Specific definitions of adverse events that should be promptly reported to the IRB differ by clinic site. Each clinic should consult with their own IRB to determine when an adverse event should be promptly reported, as opposed to reported at the following continuing review. In general, adverse events that require prompt reporting are those that indicate a new or increased risk of something related to the treatment. However, for specific indications, each clinic should consult with their own IRB.

Chapter 33: Data Safety Monitoring Committee

Data Safety and Monitoring Plan

To maintain subject safety throughout a clinical trial, an independent group of experts are appointed as a DSMC, to guide the design and monitor all aspects of the trial, including reviewing accumulated data to identify evidence of benefit, risk, or lack of treatment effect. The function of the DSMC is to make recommendations to the National Eye Institute, the Executive Committee, and the local IRBs regarding issues relevant to the safe and appropriate conduct of the trial. To this end, the DSMC will determine the data monitoring plan to be followed throughout the trial and ensure adherence to the plan. Among the responsibilities of the DSMC are the following:

- Reviewing the study design, recruitment methods, and informed consent and data collection procedures, and recommending protocol changes as deemed appropriate;
- Monitoring the trial conduct, recruitment and retention rates, and the clinic and the DCC performance;
- Evaluating data as it accumulates to monitor for harmful or beneficial effects, or assess for futility;
- Reviewing adverse events reported throughout the trial;
- Approving primary manuscripts for appropriateness and accuracy of scientific methods; and
- Approving ancillary studies to protect the scientific integrity of the trial, determining when data should be released.

Voting DSMC members, including the DSMC chair, will be appointed by the Director of the National Eye Institute or someone designated by the Director. The five voting members may include epidemiologists, biostatisticians, clinical trial specialists, clinicians, and public representatives. Members will be selected for their experience, knowledge of clinical trial methodology, and absence of conflicts of interest. Ex-officio members (non-voting) may include NEI program staff, Dr. Walline as the Study Chair and Dr. Jones-Jordan, as the Director of the Data Coordinating Center at the discretion of the voting members of the DSMC.

Chapter 34: BLINKLink Phase

The first subject enrolled in the BLINK Study will complete the randomized clinical trial approximately 20 months before the last subject enrolled due to the time required to recruit 294 subjects. In order to keep subjects engaged, so they will continue to participate in the BLINK2 Study, we will initiate the BLINKlink Phase. During the BLINKlink Phase, subjects will be examined every six months until all subjects complete the BLINK Study. When the last subject completes the BLINK Study, we will begin the BLINK2 Study if funding is awarded by the National Eye Institute.

During the BLINKlink Phase, subjects will attend visits every six months, and they will continue to receive the same contact lenses, solutions, eye examinations, and spectacles that they received during the BLINK Study. The visit window will continue to be based upon the day they were randomly assigned to a treatment group during the baseline visit of the BLINK Study. Subjects will undergo annual comprehensive eye examinations with cycloplegia, just as they have throughout the BLINK Study. Not all subjects will receive the same amount of follow-up during the BLINKlink Phase; some will complete 18 months of follow-up during the BLINKlink Phase, and some will be enrolled directly into the BLINK2 Study after completion of the BLINK Study.

Outcome Measures

The BLINKlink Phase examination procedures will be conducted as outlined in Table 34-1. Visits 10 and 12 are the 42 and 54 month visits, respectively. Visit 11 is the 4 year visit. Some subjects will complete all three visits during the BLINKlink Phase, and some subjects won't complete any visits during the BLINKlink Phase (Figure 34-1).

Table 34-1: Schedule of measurements for the BLINKlink Phase.

| | Visits 10, 12 | Visit 11 |
|--|---------------|----------|
| History Form | X | X |
| Spherical over-refraction (OU) | X | X |
| High contrast VA (OU) | X (CL) | X (CL) |
| Low contrast visual acuity (OU) | X (CL) | X (CL) |
| Near visual acuity (OU) | X (CL) | X (CL) |
| Modified Thorington | | X (CL) |
| Acc lag with CL, near (OD) | | X |
| Contact lens centration, movement (OU) | X | X |
| Choroidal thickness (OD) | | X |
| Slit lamp examination (OU, no contact lens) | X | X |
| Pupil size (OD) | | X |
| Non-cycloplegic autorefraction (OU) | X | X |
| Manifest refraction (OU) | | X |
| Cycloplegic autorefraction (1° outcome, OU)* | | X |
| Axial length (OU)* | | X |
| Intraocular pressure (OU)* | | X |
| Dilated fundus examination (OU)* | | X |
| Contact Information Form | | X |
| PREP2 Form | X | X |
| CISS Form | | X |
| Contact Lens Form | X | X |
| Parent Compliance Form | X | X |
| Length of visit (hours) | 0.75 | 1.5 |

■ = masked measure; CL = contact lens; * = cycloplegic; Acc = accommodative

Figure 34-1. Timing of the first and last child enrolled in the BLINK Study through the BLINK2 Study.

| | | | | | | | | | | | | | | | | | |
|----------------------|-------------|------|-------|------|-------|------|-----------------|------|-------|------|--------------|------|-------|------|-------|------|-------|
| First child enrolled | BLINK Study | | | | | | BLINKlink Phase | | | | BLINK2 Study | | | | | | |
| Last child enrolled | BLINK Study | | | | | | | | | | BLINK2 Study | | | | | | |
| Dates (MM/YY)* | 10/14 | 4/15 | 10/15 | 4/16 | 10/16 | 4/17 | 10/17 | 4/18 | 10/18 | 4/19 | 10/19 | 4/20 | 10/20 | 4/21 | 10/21 | 4/22 | 10/22 |

*These timelines are approximate
BLINK Study: 3 years, children wear their study contact lenses
BLINKlink Phase: time varies, children continue wearing the same contact lenses
BLINK2 Study: 3 years, all children will wear the same contact lenses

Consenting

Subjects and parents will review and sign the assent parental permission forms, respectively, during Visit 9 in the BLINK Study. If they choose to not participate in the BLINKlink Phase, then they will not be contacted to participate in the BLINK2 Study. Subjects who complete the BLINK Study within six months of beginning the BLINK2 Study will not be consented for the BLINKlink Phase; they will simply be consented for the BLINK2 Study during Visit 9.

Visit Windows

Visit windows are the time period during which a subject should be examined. The date of visits during the BLINKlink Phase are scheduled based on the date of receiving the randomization assignment. 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 during the BLINKlink Phase are shown in Table 34-2. Some subjects will complete all three visits, and some subjects will not complete any of the visits during the BLINKlink Phase.

Table 34-2: Visit windows for the BLINKlink Phase.

| Visit | Target Window (Day) | Acceptable Window (Days) |
|-------|---------------------|--------------------------|
| 10 | 1,275 | 1,245-1,305 |
| 11 | 1,455 | 1,425-1,485 |
| 12 | 1,635 | 1,605-1,665 |

Glasses

At the closeout of the BLINK Study, all subjects were to receive a prescription for glasses, but no materials. As an incentive to continue participation, subjects will continue to receive glasses at no or reduced cost at each annual visit, including Visit 9 of the BLINK Study.

If subjects lose or break their spectacle frames, new ones will be provided by the study if they are not covered by 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, the subject pays \$50 for the pair of glasses. If a subject desires transitions lenses, clip-on sunglasses, or any other item that costs extra, the subject pays retail cost for the extra item(s).

Forms

All forms for the BLINKlink Phase 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 34-3).

Table 34-3: Forms used at each visit during the study.

| Forms | Completed by | Visits 10, 12 | Visit 11 |
|--|--------------------|------------------|----------|
| Contact Information – paper <i>Do not send!</i> | Parent/Guardian | Update | Update |
| History – paper <i>Do not send!</i> | Parent/Guardian | | Update |
| Semiannual Examination | Unmasked examiner | X | |
| Annual Examination | Unmasked examiner | | X |
| Annual Masked | Masked examiner | | X |
| Contact Lens | Subject | X | X |
| PREP2 | Subject | X | X |
| CISS | Subject | | X |
| Parent Compliance | Parent/Guardian | X | X |
| Unscheduled Visit – as needed | Unmasked examiner | | |
| Discontinuation – as needed | Unmasked examiner | | |
| Adverse Event – as needed | Unmasked examiner | | |
| Crossover – at time of crossover | Unmasked examiner | | |
| Calibration – monthly | Clinic Coordinator | | |

Chapter 35: Bibliography

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Chapter 36: MOP Changes

Table 35-1: Changes to Manual of Operating Procedures approved after initial approval.

| Date Approved | Description |
|---------------|---|
| 7/3/14 | Version 1.0 approved |
| 7/29/14 | Page 33, #12: Replaced “Obtain at least five readings without the “retry” message. When in doubt, take additional measurements to ensure that at least 5 “good” measurements exist” with “Obtain at least five “good” readings in which neither the sphere nor cylinder differ from the mode by more than 1.00 D. When in doubt, take additional measurements to ensure that at least 5 “good” measurements exist.” |
| 7/29/14 | Page 67, #11: Replaced “Obtain at least five readings without the “retry” message. When in doubt, take additional measurements to ensure that at least 5 “good” measurements exist” with “Obtain at least five “good” readings in which neither the sphere nor cylinder differ from the mode by more than 1.00 D. When in doubt, take additional measurements to ensure that at least 5 “good” measurements exist.” |
| 7/29/14 | Page 26: Added “14. Record the number of letters read correctly and the test distance in REDCap.” |
| 7/29/14 | Page 68: Table 24-1: Replaced “Unmasked Examiner” with “Parent/Guardian” for person to complete History and Contact Information Forms. |
| 7/29/14 | Page 49: Include, “The date will be the date of the download. 7. Click Next . The Lenstar will give you a prompt that the report was generated successfully.” and “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.” |
| 7/29/14 | Pages 84 and 85: Remove Chapter 32: Study Forms |
| 7/29/14 | Page 36: Changed the Equipment section to read: “Measurement of pupil diameter is performed using the NeuroOptics VIP-200 Pupillometer (NeuroOptics, 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 during contact lens wear. Measurements should be performed at Visits 1, 5, 7, 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. 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).” |
| 7/29/14 | Page 48: corrected the gaze and corresponding retina, and made the order the same as will be measured. |
| 7/29/14 | Page 15: Added + Acc Lag (Visit 1) to Table 8-2. |
| 7/29/14 | Page 27: Changed what to wear after the over-refraction from new lens power to spherical over-refraction in trial frame and habitual contact lens |
| 7/29/14 | Page 34: Remove depth from corneal staining description |
| 7/29/14 | Page 72: Allowed Contact Information Form to be maintained in subject binder instead of separate file. |
| 7/29/14 | Page 47: Add accommodative lag chapter |
| 7/29/14 | Page 36: Added that the light which should be pointed straight down toward the examination chair during the mesopic condition. |
| 7/29/14 | Page 74: Added, “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.” |
| 7/31/14 | Page 15: Moved Choroidal Thickness in Table 8-2 to right after contact lens movement |

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|----------|--|
| 7/31/14 | Chapter 20: Clarified lag measurement at baseline protocol |
| 7/31/14 | Page 14: Removed "at near" from VA requirement with +2.50 add |
| 7/31/14 | Chapter 26: Added chapter on contact lens insertion, removal and care |
| 7/31/14 | Page 15: Moved Choroidal Thickness in Table 8-2 from Visit 1 to Visit 2 |
| 8/25/14 | Page 56: Changed "22" to "18" because of mis-numbering |
| 8/25/14 | Page 37: Changed first visit OCT is performed to Visit 2 instead of Visit 1 |
| 8/25/14 | Page 34: Changed slit lamp grading to Efron scale for all slit lamp signs |
| 8/25/14 | Pages 38-44: Replaced Chapter 18 to improve clarity of procedure and include uploading information |
| 8/25/14 | Page 7: Added Maria Walker to Study Group and dates of participation |
| 8/25/14 | Page 60: Add how to upload file into REDCap |
| 2/13/15 | Page 14: Added, "If a subject is ineligible, the Study Completion Form should be completed (in REDCap) with the reasons for the ineligibility." |
| 2/13/15 | Page 19: Added, "At this time, complete the discontinuation section of the Study Completion Form in REDCap." |
| 2/13/15 | Pages 34, 58, 59, and 72: change "mode" to "median" for ridding autorefractor readings of errant values. |
| 2/13/15 | Page 26: added section "High Contrast Monocular Visual Acuity at Baseline |
| 2/13/15 | Page 48: stated that forehead rest should be used during central autorefraction. |
| 2/13/15 | Page 88: add a section stating how it will be determine whether or not an Adverse Event Form should be completed, and who will make the final determination of whether or not it is an Adverse Event. |
| 2/16/15 | Page 28: trial lenses should be used to conduct an over-refraction instead of a phoropter. |
| 3/18/15 | Page 35: Changed the wording about when an adverse event report should be completed to match the adverse event chapter. |
| 8/21/15 | Page 67: Replaced steps 7-10 with updated text. |
| 9/1/15 | Page 60: Changed analysis diameter in COAS from 5 mm to 6 mm |
| 11/30/15 | Page 7: Updated study personnel |
| 12/14/15 | Pages 97-89: Replace chapter on adverse events to make categorization more clear |
| 12/29/15 | Page 15: CISS will be completed only at Visits 1, 3, 4, 5, 7, and 9 |
| 2/18/16 | Table 25-1: CISS will be completed only at Visits 1, 3, 4, 5, 7, and 9 |
| 3/24/16 | Page 53: Added, "Any reading on the Lenstar that is highlighted in red is not valid. Readings highlighted in red must be deleted and, if possible, replaced with a valid reading. If it is not possible to obtain five valid readings for a measurement location, a protocol deviation form should be completed, documenting that readings highlighted in red were deleted and could not be replaced with valid ones." |
| 6/2/16 | Page 46: Added tetracaine |
| 10/13/16 | Page 83: Added section on protocol for submitting manuscripts |
| 10/13/16 | Page 88: Added section on prompt reporting of adverse events to IRB |
| 10/13/16 | Page 12: Updated personnel |
| 1/3/17 | Page 27: Allowed for phoropter to be used for over-refraction |
| 1/30/17 | Page 83: Included grant support from UH Core Grant in acknowledgments (P30-EY007551) |
| 5/4/17 | Page 7: Added Lea Hair to the study group |
| 5/18/17 | Page 90: Inserted Chapter 34: BLINKlink Phase |
| 5/18/17 | Page 91: Changed Chapter 34: Bibliography to Chapter 35: Bibliography |
| 5/18/17 | Page 92: Changed Chapter 35: MOP Changes to Chapter 36: MOP Changes |
| 5/31/17 | Page 7: Updated study personnel |
| 7/31/17 | Page 7: Updated study personnel |

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|---------|---|
| 8/23/17 | Page 7: Updated study personnel |
| 8/29/17 | Page 83: Included grant support from UH Core Grant in acknowledgments (UL1 TR 001070) |
| 5/18/18 | Page 7: Updated study personnel |