On-Eye Optical Quality of Lotrafilcon B Lenses Over 12 Hours

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TITLE: ON-EYE OPTICAL QUALITY OF LOTRAFILCON B LENSES OVER 12 HOURS

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INVESTIGATION SITE: Indiana University

STUDY OVERVIEW

The optical aberrations and resultant visual quality of a contact lens wearer is influenced by several factors such as the optics of the eye, pre- and post-contact lens tear film, contact lens material, water content, and the lens design. Previous studies have evaluated the optical quality of soft contact lenses off of the eye (e.g. Kollbaum 2004) and on the eye (e.g. Kollbaum 2007). A previous study by Montes-Mico (Montes-Mico 2012) also evaluated the optical quality of soft contact lenses, focusing on the change in on-eye optical contact lens aberrations throughout the day. They found that some lenses had relatively little change across the day, whereas other lenses had greater changes, presumed due to contact lens surface and lens bulk dehydration. This study, however, had limited published details making modeling and predictions based on the results not possible. The study also used an incomplete set of lenes compared to what is currently in the marketplace. The current study aims to systematically investigate the diurnal variation in the optical quality of soft contact lenses on eye throughout the day. Subject reported quality of vision will also be evaluated.

PROTOCOL SYNOPSIS

KEY OBJECTIVE	1. Diurnal variation within lens in the on-eye optical quality of soft lenses over time (12 hours) 2. Subject reported within-lens vision stability over time (0-100 scale)
KEY ENDPOINTS /OUTCOME MEASURES	Key endpoints are the monocular (OD only) responses of: 1. *RMS.* RMS (total and higher-order) only, will be compared across time and between lenses. From these measures of RMS, change over time can be quantified as a magnitude and percentage. 2. *Root Mean Square (RMS) Fit Error.* For each optical measurement, the wavefront will be reconstructed using both a 'typical' modal (Zernike) reconstruction and zonal (local integration) reconstruction. The difference between these two reconstructed wavefronts constitutes an estimate of the RMS fit error (how much error is introduced from the "real wavefront" (local is closest approximation) relative to the Zernike modally fit wavefront. 3. Subject reported within-lens vision stability over time (0-100 scale, viewing distant target)

STUDY DESIGN	The study is a monocular (only OD measured, matching type of correction for OS), subject masked, 2 x 2 randomized, crossover (with an additional non-randomized baseline reference (3 arms in all)) comparing the within-lens difference in diurnal (AM to PM) change in optical quality with different soft lenses relative to the diurnal change at baseline (no lens). Subjects will be tested for and must meet all inclusion criteria and not meet any exclusion criteria prior to beginning lens testing. Lens wearing protocol: 1. Subjects will first have measurements acquired every 2±0.5 hours for 12 hours without any lenses (no lens, baseline). The subject will wear their habitual spectacles between measurement periods. 2. Following a day of washout with spectacle wear only each type of lens will be used in both eyes for a period of 2±1 days. Early the following morning, the subject will present to the clinic wearing spectacles. A lens of the same type they have been wearing for the previous 2±1 days will be insterted while a masked examiner then performs measurements every 2±0.5 hours for 12±1 hours. Measurements will include monocular aberrometry (minimum 5mm analysis diameter), Medmont topography, and subjective measures. (0-100 scale). 3. Subjects will then be dispensed the next randomized lens pair and told to not wear the lens that day or the following (washout) day, but the next 2±1 days. As previous, the subject will present to the clinic on the third day not wearing the lenses. Lenses will be inserted, and then measures will be taken throughout the day. Measurement protocol: 1. At the beginning of each testing day, measures of the subject's eye alone will be captured. This will serve as 'baseline' for each day. 2. The study lenses will then be inserted acrording to the lens randomization schedule. 4. Following 10-20 minutes of lens settling, eye+lens aberrometry (minimum 5mm analysis diameter) and subjective measures (0-100 scale) will be acquired. 3. This cycle will be repeated every 2±0.5 hours up to 12±1 hours. 4. At the end of 12±1 hours, the subject will return all lenses of that set, and be given the next set of lenses to repeat the washout, wearing, and measurement cycle. Dilation Protocol: No pharmacological dilation will be used in this study. Subjects will be in a dark room aiming to achieve a natural pupil diameter of at least 5 mm. Upon inclusion, if a subject cannot

	achieve a non-dilated pupil diameter of at least 5 mm, they will be excluded from the study. If a subject meets a 5 mm pupil on most time points of both sets of lenses, but not all, inclusion of data acquired smaller than 5 mm will be scaled to 5 mm and considered on an individual basis. Equipment: 1. An aberrometer (e.g. COAS-HD, CSO Osiris) will be used for all optical measures. The aberration data will be obtained for central 3- and 5-mm diameter areas. Wavefront data will be recontstructed by both modal (up to 6th order Zernike polynomials) and zonal (local slope) methods.
Sample size	Complete N=21, enroll up to N=24
Hypothesis	1. The Air Optix plus Hydraglyde lens will have levels of variation in aberration throughout the day not significantly different than the naked eye. 2. The Air Optix Aqua lens will have levels of variation in aberration throughout the day not significantly different than the naked eye. 3. The Air Optix plus Hydraglyde lens will have lower variation in aberration throughout the day relative to the Air Optix Aqua lenses.
TEST COMPARATOR PRODUCTS	Baseline = Naked eye Lenses: Set of soft lenses 1. Air Optix plus Hydraglyde on daily disposable basis 2. Air Optix Aqua on daily disposable basis (ALCON will provide lenses)
INCLUSION/EXCLUSION CRITERIA	1. Habitual prescription within the range of +5.00 D to -6.00 D 2. 18-35 years of age 3. No history of issues of eye alignment or binocularity by self-report 4. No doctor diagnosed, self-reported accommodative or binocular vision issues 5. No doctor diagnosed, self-reported ocular surface disease or dry eye requiring regular, ongoing treatment 6. The subject must appear able and willing to adhere to the instructions set forth in this clinical protocol. 7. Vertex corrected refractive cylinder must be -0.75 or less. 8. Visual acuity best correctable to 20/25 or better for each eye 9. The subject must read and sign the Informed Consent form. 10. No active conditions that may prevent soft contact lens wear. 11. Mesopic pupil size >5.00 mm.
OFF LABEL	No.
CLINICAL SUPPLIES REQUESTED FROM ALCON	Trial set of soft contact lenses for each of the following 1. Air Optix plus Hydraglyde on daily disposable basis 2. Air Optix Aqua on daily disposable basis (ALCON will provide all lenses)
RESULTS DISSEMINATION	Work will be presented at least one international meeting, such as Global Specialty Lens Symposium, ISCLR, or ARVO. Trade or peer-

	reviewed publications will be prepared at Sponsor's request and expense.
CONFLICT OF INTEREST	None.

PROPOSAL SUMMARY

STUDY DURATION	Contract approval: unknown, estimate 1 month Human subjects approval: 1 month, concurrent to above Project setup: 1 month, concurrent to above Recruitment: 1 month, concurrent to above Data collection: 2 months Data analysis: 1 month Report writing: 1 month Contract for 1 year to account for any delays or necessary subsequent analyses.
DURATION OF IRB	1 year
GCP TRAINING	Received; 2015-03-14
TYPE OF STUDY	Single center
OTHER FUNDING	None

RATIONALE AND SIGNIFICANCE:

The optical aberrations and resultant visual quality of a contact lens wearer is influenced by several factors such as the optics of the eye, pre- and post-contact lens tear film, contact lens material, water content, and the lens design. Previous studies have evaluated the optical quality of soft contact lenses off of the eye (e.g. Kollbaum 2004) and on the eye (e.g. Kollbaum 2007). A previous study by Montes-Mico (Montes-Mico 2012) also evaluated the optical quality of soft contact lenses, focusing on the change in on-eye optical contact lens aberrations throughout the day. They found that some lenses had relatively little change across the day, whereas other lenses had greater changes, presumed due to contact lens surface and lens bulk dehydration. This study, however, had limited published details making modeling and predictions based on the results not possible. The study also used an incomplete set of lenes compared to what is currently in the marketplace.

AIM: The current study aims to systematically investigate the diurnal variation in the optical quality of soft contact lenses on eye throughout the day. Subject reported quality of vision will also be evaluated.

STUDY DESIGN

The study is a monocular (OD only), subject masked, 2 x 2 randomized, crossover (with an additional non-randomized baseline reference (3 arms in all)) comparing the difference in diurnal change in optical quality with different soft lenses relative to baseline (no lens).

Lens wearing protocol:

1. Subjects will first have measurements acquired every 2±0.5 hours for 12±1 hours without any lenses (no lens, baseline). The subject will wear their habitual spectacles between measurement periods.
2. Following a day of washout with spectacle wear only, each type of lens will be used in both eyes for a period of 2±1 days. Early the following morning, the subject will present to the clinic wearing spectacles. A lens of the same type they have been wearing for the previous few days will be insterted while a masked examiner then performs measurements every 2±0.5 hours for 12±1 hours.
3. Subjects will then be dispensed the next randomized lens pair and told to not wear the lens that day or the following (washout) day, but the next two days. As previous, the subject will present to the clinic on the third day not wearing the lenses. Lenses will be inserted, and then measures will be taken throughout the day.

Measurement protocol:

1. At the beginning of each testing day, aberrometry, Medmont topography (non-invasive tear break-up), and subjective quality measures of the subject's OD eye alone will be captured. This will serve as 'baseline' for each day.
2. The study lenses will then be inserted acrording to the randomization schedule.
3. Following 10-20 minutes of lens settling, eye+lens aberrometry (minimum 5 mm analysis diameter, Medmont corneal topography, and subjective (0-100 scale) measures will be acquired on the OD. Measures of contact lens position (through recorded imaging) will also be performed. Measures at this time point will serve as "time 0" for each lens wearing day.
4. This cycle will be repeated every 2±0.5 hours up to 12±1 hours.
5. At the end of 12±1 hours, the subject will return all lenses of that set, and be given the next set of lenses to repeat the washout, wearing and measurement cycle.

Dilation Protocol:

No pharmacological dilation will be used in this study. Subjects will be in a dark room aiming to achieve a natural pupil diameter of at least 5 mm. Upon inclusion, if a subject cannot achieve a non-dilated pupil diameter of at least 5 mm, they will be excluded from the study. If a subject meets a 5 mm pupil on most time points/lenses, but not all, inclusion of data acquired smaller than 5 mm will be scaled to 5 mm and considered on an individual basis.

Equipment:

1. An aberrometer (e.g. COAS-HD or CSO Osiris) will be used for all optical measures. The aberration data will be obtained for central 3- and 5-mm diameter areas. Wavefront data will be recontstructed by both modal (up to 6th order Zernike polynomials) and zonal (local slope) methods.
2. A Medmont corneal topographer will be used following each set of aberration measures to also monitor the tear film upon the eye/contact lens.

SUBJECTS

Sample Size:

This section describes the rationale and approach used to establish the minimum sample size (N) needed to achieve 80% power at a nominal significance level α=0.05 for detecting a mean difference between percentage change in RMS of higher-order wavefront aberrations measured over a 12-hr period for the test lenses and the percentage change observed without a contact lens (no-CL). For each subject and lens, a series of five RMS measurements will be obtained at 0 hours (baseline) and at six, 2-hr intervals within each period. Technically, the statistical power for testing the contact lens main effect will depend not only on the structure of the covariance matrix but also on how the baseline measurements recorded at time=0 hours are incorporated into the statistical model(s). But, given the degree of uncertainty about the input parameter values required to estimate sample size, we believe it reasonable to base initial calculations on a dependent sample t-test on a mean difference score under the assumption of no differential carryover effect. Thus, the target parameter of interest for our primary analysis corresponds to the true difference in the mean post-baseline percentage change over 12 hours between each of the test contact lenses and no-CL for N subjects. Note that this test would be equivalent to testing the interaction of “lens” and “hours of use” factors in a two-way repeated measurements ANOVA.

Data was not available on the two test lenses, so we used previously published data on an ALCON lens expected to provide similar responses. Specifically, we approximated parameter values for [1] effect size, [2] within-subject variance, and [3] within-subject correlation from the data reported in two previous studies. Specifically, Montes-Mico, *et al* (2013) measured wavefront aberrations in 15 myopic eyes before and at 2-hr intervals after contact lens fitting over a 12-hr period. Using the 5-mm pupil diameter data presented in Figure 2 of the referenced paper, we estimated that the group-averaged percentage change between the baseline (i.e., 2-hr after lens fitting) and the final measurement (i.e., after 12-hr wearing time) of ~3% and ~5% for no-CL and DAILIES TOTAL ONE (DT1) lens, respectively. Note that this difference between no-CL and DT1 was smaller than any of the other lenses under test, but mirrors the expectation for the current test lenses. To allow for mean differences larger than the observed 2% mean difference between each of the test lenses and no-CL in the current study, we added a 1.5% non-inferiority margin; thus, our sample size calculation assumes a ‘null difference’ of 3.5%.

Our within-subject variability and correlation estimates were taken from Cheng, *et al* (2004) who reported on the stability of clinical monochromatic aberrometry measurements over a wide range of time scales. First, temporal variability of wavefront root mean square (RMS) error, excluding defocus and astigmatism, was tracked across five repeated measurements for 4 subjects at four different time scales. The averaged variance estimates for different time scales ranged from 8.10 x 10^{-5} μm^2 (t < 1 second) to 9.73 x 10^{-4} μm^2 (t < 1 year). For our calculations, we used their reported value of 4.41 x 10^{-4} μm^2 (t < 1 week) as our variance estimate, which translates to a standard deviation of 2.1%. We expect that this is a worst-case scenario because the value was derived by calculating the between-day variances for individual trials across five days for each subject and then calculating the average across the four subjects and five trials on each day. Our data will be multiple measurements taken within a 12-hr period on the same day. Second, Cheng, *et al* (2004) reported a within-subject correlation estimate of r=0.799 that was based on a linear regression analysis of the higher-order RMS error measurements over a one-year time scale for subject AB. Again, because the time-scale in the current study proposal is only 12 hours (i.e., is much shorter than 1 year), we expect that the magnitude of the within-subject correlation in our sample is likely to be 0.80 higher. For purposes of the sample size calculation, we used three values for the correlation parameter, i.e., r = {0.70, 0.75, and 0.80}. The input parameters for this sample size calculation scenario are shown in Table 1(a). The actual power and number of paired observations for this scenario are presented in Table 1(b) and were obtained using SAS 9.4 by varying both the mean difference and the correlation parameters.

Table 1 (a)

Fixed Scenario		
Distribution	Normal	
Method	Exact	
Number of	L	
Null	3.50	%
Alpha	0.05	
Standard	2.10	%
Nominal	0.80	

Table 1 (b)

Index	Mean Diff	Corr	Actual Power	N Pairs
1	2.00	0.70	0.810	9
2		0.75	0.822	8
3		0.80	0.838	7
4	2.25	0.70	0.802	12
5		0.75	0.829	11
6		0.80	0.824	9
7	2.50	0.70	0.804	18
8		0.75	0.822	16
9		0.80	0.819	13
10	2.75	0.70	0.806	31
11		0.75	0.805	26
12		0.80	0.803	21
13	3.00	0.70	0.801	67
14		0.75	0.801	56
15		0.80	0.808	46

Note that the paired-sample t test assumes normally distributed data and requires N ≥ 2. The test statistics are

$$t = N^{1/2}\left(\frac{\bar{d}-\mu_0}{s_d}\right) \sim t(N-1,\delta) \text{ or, equivalently, } t^2 \sim F(1,N-1,\delta^2)$$

where $\bar{d}$ and s_d are the sample mean and standard deviation of the differences, and

$$\delta = N^{1/2}\left(\frac{\mu_{diff}-\mu_0}{\sigma_{diff}}\right) \text{ and } \sigma_{diff} = (\sigma_1^2 + \sigma_1^2 - 2\rho\sigma_1\sigma_2)^{1/2}$$

represent the non-centrality parameter and standard deviation of the paired difference scores, respectively. In order to compensate for potential data loss due to subject attrition, we propose increasing the targeted sample size of N=21 to 24 which is based on a post-consent/randomization attrition rate between 5 and 10% observed in 50+ studies in our laboratory that have required multiple (>1) daytime visits.

Inclusion Criteria:

1. Habitual prescription +5.00 D to -6.00 D
2. 18-35 years of age
3. No history of issues of eye alignment or binocularity by self-report
4. No doctor diagnosed, self-reported accommodative or binocular vision issues
5. No doctor diagnosed, self-reported ocular surface disease or dry eye requiring regular, ongoing treatment
6. The subject must appear able and willing to adhere to the instructions set forth in this clinical protocol.
7. Vertex corrected refractive cylinder must be -0.75 or less.
8. Visual acuity best correctable to 20/25 or better for each eye
9. The subject must read and sign the Informed Consent form.
10. No active conditions that may prevent soft contact lens wear.
11. Mesopic pupil size >5.00 mm.

LENSES

Lens powers are based on vertexed (15 mm) spherical equivalent refraction (performed upon study entry) and matched between all lens types.

1. Baseline no lens
2. Air Optix plus Hydraglyde on daily disposable basis
3. Air Optix Aqua on daily disposable basis

(*ALCON supplies all lenses)

OUTCOME MEASURES

Primary:

The primary outcome measure in this study will be a derived variable indexing the percentage change in the RMS of higher-order wavefront aberrations (microns) at a 3 and 5 mm pupil from baseline to 12 hours. For each participant, we will convert the data from microns into the percentage change in RMS, $\%\Delta_{i(12\text{-}0)k} = 100 \times (RMS_{i12k} - RMS_{i0k})/RMS_{i0k}$ where i=1,2,..,N participant, j represents time (hrs) Є (0 (BL) , 2, …, 12), and k denotes lens. Our initial analysis will compare the mean $\%\Delta_{\cdot(12\text{-}0)test}$ computed across N participants for each of the Air Optix plus Hydraglyde and Air Optix Aqua lenses independently with the mean $\%\Delta_{\cdot(12\text{-}0)NCL}$ with no contact lens.

Secondary:

1. *Subject-reported vision-stability (0-100 scale, while viewing at distance)*
2. *Root Mean Square Fit Error.* For each optical measurement, the wavefront will be reconstructed using both a 'typical' modal (Zernike) reconstruction and zonal (local integration) reconstruction. The difference between these two reconstructed wavefronts will be evaluated.

TESTING PROCEDURES:

In office testing will be done at study entry, and following 2±1 days of lens wear for each of the follow up visits.

Testing Day 1, Visit 1 Baseline/Inclusion:

1. Demographics
2. Ocular history
3. Entrance Snellen visual acuity
4. Entrance ocular health (with conjunctival and corneal staining)
5. Habitual lens information (type, power)
6. Habitual lens use (wearing schedule, replacement schedule, hours per day, insertion time, removal time)
7. Subjective refraction (best objective with an additional -0.25 D for subjective improvement)
8. Fit evaluation of all lens pairs. If all lens pairs do not fit adequately enough per investigator clinical determination for dispensing, subject will be exited from the study.
9. Snellen acuity of each eye for all lens pairs.

Testing Day 2, Visit 1-7 Naked eye diurnal measures:

1. Subjects will first have aberrometry, Medmont topography, and subjective quality measurements acquired every 2±0.5 hours for 12±1 hours without any lenses (no lens, baseline). The subject will wear their habitual spectacles between measurement periods.

Testing Day 3, Visit 1-7 and Testing Day 4, Visit 1-7 (each separated by a day of washout and 2±1 days of study lens wear):

1. At the beginning of each measurement day, aberrometry, Medmont topography, and subjective quality measures of the subject's eyes alone (COAS and Medmont) will be captured. This will serve as 'baseline' for each day (for the spectacle day, this will also be "time 0").
2. The study lenses (or no lens for spectacle day) will then be inserted acrording to the randomization schedule.

3. Following 10-20 minutes of lens settling, the eye+lens aberrometry (minimum 5 mm analysis), Medmont topography, and subjective quality (0-100 scale) measures will be acquired for each eye. This will serve as "time 0" for each lens wearing day.
4. This cycle will be repeated every 2±0.5 hours up to 12±1 hours.
5. At the end of 12 hours, the subject will return all lenses of that set, and be given the next set with a schedule of washout and wear days.

Testing Day 4, Visit 7 = Exit:

1. Exit ocular health (with conjunctival and corneal staining)
2. Exit Snellen visual acuity

STATISTICAL ANALYSIS

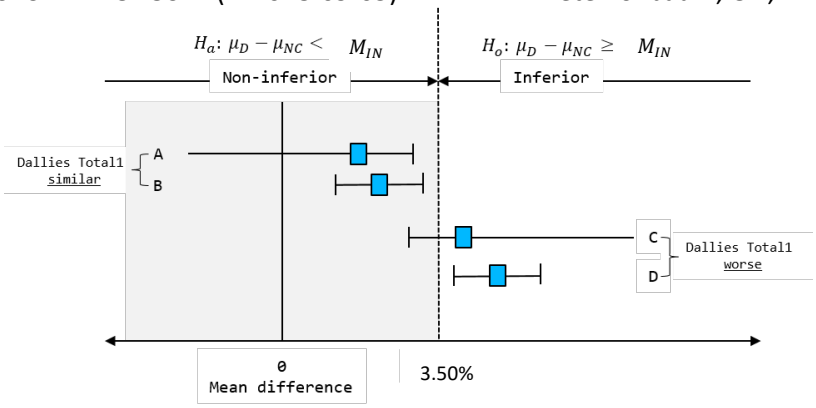
Separate tables with descriptive statistics will be provided for all baseline, outcome/endpoint and safety variables, as appropriate. Continuous variables will be summarized with location and dispersion parameter estimates while categorical data will be summarized using frequency counts, percentages and margin tables where appropriate. Visualizations and related graphs will be provided in support of these data summaries.

Statistical analyses will be performed only after all data have been collected, transcribed into the electronic database, and error checked and corrected if needed. We will first test for a differential carryover effect of lens using a linear (ANOVA) model. For a crossover design, the model can be expressed as

$$y_{ijkl} = \mu + \alpha_i + \rho_{j(i)} + \gamma_k + \tau_l + \lambda_m + \gamma\tau_{kl} + e_{ijkl}$$

where μ is the overall mean, α_i is the effect for the *i*th sequence, $\rho_{j(i)}$ is the random effect for the of the *j*th individual within the *i*th sequence (i.e. $\rho_{j(i)} \sim N(0, \sigma_\rho^2)$, $\gamma_k$is the effect of the *k*th period, τ_l is the effect of the *l*th lens effect and λ_m is the effect of the *m*th carryover effect with e_{ijkl} being the NIID residual term (i.e., $e_{ijkl} \sim N(0, \sigma_e^2)$. Assuming that there is no statistical evidence of a period x lens interaction ($\gamma\tau_{kl}$), we will use a <u>one-sided</u> equivalence (i.e., non-inferiority) test to determine whether the average percentage increase in higher-order RMS induced by Dailies1 Lens is no worse than the average increase without a contact lens. In practice we can use a single directional paired-sample t-test to test the null hypotheses. If we reject H_o we should conclude that the percentage increase over a 12-hour period in higher-order RMS induced by each of the test lenses is no worse than the increase measured without a contact lens. In this context, smaller differences in the mean difference in higher-order RMS are "better." Thus, the statistical hypotheses are arranged so that rejecting the null hypothesis for the specified null difference implies that, the observed mean change over 12 hours for each of the test lenses is not significantly worse than the mean change with no-CL. i.e.,

$$H_o: \mu_D - \mu_{NC} \geq M_{IN} \text{ versus } H_a: \mu_D - \mu_{NC} < M_{IN}$$



Interpretation of non-inferiority test of the Dallies Total1 (test) to the reference non-contact lens (active control). Shaded area represents the non-inferiority range. Hypotheses are arranged so that larger mean difference values lead to rejection of the null hypothesis. ▮= observed point estimate of mean difference; both A and C show 1-sided confidence intervals; B and D show 2-sided CIs. Both A and E imply that Dallies Total1 is non-inferior to active non-contact lens control because the entire CI is below non-inferiority margin (3.25%). C and D imply the Dallies is inferior although a larger sample is needed to shrink the CI so that the entire interval C falls in the region of inferiority.

Second, a comparison of the statistic $\%\Delta_{i(12\text{-}0)test}$ for one test lens with $\%\Delta_{i(12\text{-}0)k\text{-}1}$ the other test lens in the study will be performed by fitting a linear mixed effects regression model with restricted maximum likelihood (REML) estimation. The effect of lens will be parameterized in this model with (0,1) GLM dummy coding using Air Optix with Hydraglide as the reference lens; thus, a separate parameter estimate will be obtained for the other test lens. The initial model will include a single random effect for subject. We will also perform sensitivity analyses by adding covariates and refitting the model with ML to obtain 'adjusted' parameter estimates for the fixed effect of lens to account for potential confounding due to measured covariates.

PUBLICATION PLAN:

Work will be presented at least one international meeting, such as American Academy of Optometry, Global Specialty Lens Symposium, ISCLR, BCLA, American Optometric Association, or ARVO. The work will also be prepared for submission for peer-reviewed or trade publication (e.g. Optometry and Vision Science) at Sponsor's request and if results merit.

TIMELINE: (estimated)

Contract approval: unknown, estimate 1 month
Human subjects approval: 1 month, concurrent to above
Project setup: 1 month, concurrent to above
Recruitment: 1 month, concurrent to above
Data collection: 2 months
Data analysis: 1 month
Report writing: 1 month1

Contract for 1 year to account for any delays or necessary subsequent analyses.