Accommodative Relief for Uncomfortable Non-Presbyopes

Study Protocol Including Statistical Analysis Plan

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I. Objective

To determine how multifocal contact lenses affect contact lens comfort in non-presbyopic contact lens wearers.

II. Background and Rationale

Contact lens discomfort is a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear.[1] Patients with contact lens discomfort typically reports symptoms such as dryness, irritation, discomfort, and fatigue.[1] With today's growing use of digital devices, visual, ocular, and musculoskeletal (neck and shoulder pain) symptoms have been reported to include eye strain, eye fatigue, burning and irritation of the eyes, tired eyes, dry eyes, ached in and around the eyes, blurred vision at near, blurred vision when looking from near to far, headache, neck ache, and shoulder pain.[2] For contact lens wearers, prolonged use of digital devices and the decreased blink rate associated with such activities, have been suggested causes of contact lens discomfort.[3, 4] Despite the etiology, severity of dry eye clinical signs rarely correlates with severity of discomfort symptoms.[5] Because of this, treatments are focused on symptom relief alone.

Interestingly, uncomfortable contact lens wearers report symptoms very similar to patients with insufficient accommodation. Accommodation is the physiological ocular response that allows us to focus at near.[6] Similar to subjects with contact lens discomfort, patients with insufficient accommodation report symptoms like sore eyes, tired eyes, and symptoms that increase and become more intense at the end of the day.[7, 8] In a group of young, uncomfortable contact lens wearers, our laboratory found that accommodative insufficiency was unusually high and more prevalent than previously reported in the normal population.[9]

While presbyopia is a progressive, age-related condition that results in declining accommodative ability over a period of approximately 20 years,[6] most people begin to experience functional presbyopic symptoms (near blur, trouble focusing while reading, etc.) around the ages of 40-45 years.[6] In spectacle wearers, presbyopia is treated with bifocal spectacle lenses. For contact lens wearers, a multifocal contact lens may be used to treat the declining accommodation.

Considering the high prevalence of accommodative insufficiency we found in uncomfortable contact lens wearers with a mean age of 25 years,[9] it is possible that natural accommodative decline is contributing to contact lens discomfort among wearers with prolonged use of digital devices. This discomfort, or asthenopia, may be especially prevalent in contact lens wearers who are also near-sighted (myopic). Because of basic optical principles, myopic patients have to exert more accommodation when corrected with contact lenses compared to spectacles.[10] This increased demand may be bearable for a young person with adequate accommodation, but a myopic patient could experience accommodative eyestrain and fatigue when corrected with contact lenses that he or she did not experience with spectacles. This study will determine how multifocal contact lens correction affects symptoms of discomfort and asthenopia in a group of myopic contact lens wearers in the non-presbyopic age range.

III. Procedures

a. Research Design

A prospective, randomized, cross-over clinical trial will be performed.

b. Sample

Uncomfortable myopic soft contact lens wearers that fall in the non-presbyopic age group will be recruited. Table 1 lists the complete inclusion criterion. A total of 68 subjects will be recruited. See the Detailed Study Procedures section for a complete sample size justification.

Personal Characteristics	Dry Eye Status	Binocular Vision Status
30-40 years old	≤ Grade 1 ocular surface staining[12]	≤ 4 prism diopters eso or exophoria at distance and near (via Modified Thoringon)[14]
Visual acuity of 20/25 or better in each eye with habitual correction	Schirmer score ≥ 7 mm[13]	Near point of convergence ≤ 6 cm[14]
Myopic OU (-0.75 D or more myopic) Spherical OU (-0.75 D or less astigmatism (with autorefraction)	Tear break-up time (TBUT) ≥ 7 seconds[13]	No history of strabismus, patching
Soft, single vision contact lens wearer who do not currently require a reading aid (reading glasses, bifocal, multifocal contact lenses, etc.)		Reports digital device (smart phone, tablet, computer) of at least 3 hours per day
CLDEQ-8 score ≥ 12 points[11]		
No ocular surgery/medication history		
Reports digital device (smart phone, tablet, computer) of at least 3 hours per day		

Table 1: Inclusion criterion

c. Measurement/Instrumentation

All measurements and tests performed throughout this study are currently used in routine eye examinations. The risks associated with all study procedures are no more than would be encountered by the subject during a normal eye exam. All subjects will be habitual soft contact lens wearers, so no additional risk will be incurred by subjects when they are fitted into the two study contact lenses. Below is a summary of all vision tests, dry eye tests, binocular vision tests, and contact lens fitting/assessment methods that will be used throughout the study.

Visual Acuity Assessment: Distance (6 meters) visual acuity will be assessed on a high contrast visual acuity chart when the patients wears their habitual contact lenses in each eye. Patients will instructed to read the 20/25 line monocularly. Subjects who cannot read at least 3 of 5 letters on the 20/25 line with each eye will be excluded from the study.

Refractive Error Determination: Inclusion criteria refractive error will be determined using an autorefractor while the patient is not corrected with spectacles or contact lenses. This non-contact, automated instrument measures the subject's spectacle/contact lens prescription. Subjects that do not meet refractive error inclusion criteria (Table 1) will be excluded from the study.

Contact Lens Dry Eye Questionaire-8 (CLDEQ-8): The CLDEQ-8 is an eight-item questionnaire that has been validated to reflect satisfaction and change in opinion of soft contact lenses.[11] To ensure all study subjects are significantly symptomatic for contact lens discomfort, all subjects must have a score ≥12 points (show to be a score that identifies a subject that could benefit from

clinical management of contact lens-related symptoms[15]) in order to qualify for the baseline examination.

Convergence Insufficiency Symptom Survey (CISS): The CISS is a 16-item questionnaire that has been validated to assess symptoms of convergence insufficiency, a common binocular vision disorder.[16] Symptoms of contact lens discomfort and dryness are similar to convergence insufficiency symptoms,[9] so the CISS will be administered at each study visit.

Binocular Vision Testing: Binocular vision testing assesses the ability of the eyes to move, converge, diverge, and focus together while focusing at distance and near targets. Symptoms of binocular vision disorders are similar and sometimes associated with accommodative disorders. Therefore, we will exclude any subject that has significant signs of a binocular vision disorder. Binocular vision testing for this study will include horizontal heterophoria measurements, near point of convergence (NPC), and accommodative function testing. All of these tests are performed in routine eye exams.

Heterophoria Measurement: Heterophoria measurements how well the eyes simultaneously focus and align together. Several methods exist to measure heterophoria. Modified Thorington (MT) testing has been shown to be the most repeatable form,[17] so it will be used in this study at distance (6 m) and near (40 cm). A Maddox rod (transparent red occluder with cylindrical grooves) will be used to perform the technique. The MT card contacts horizontal and vertical rows of numbers that are calibrated to measure prism diopters at each distance. Each card contains a small central hole where a penlight will be shown through. The subject will hold a Maddox rod over their right eye in a horizontal orientation, and the subject will see a red streak of light while viewing the MT card. At both distance and near, the subject will be asked to report what numbered row the red streak is passing through. This number on the card corresponds to a particular horizontal heterophoria finding, which will be recorded for distance and near. Subjects reporting 4 or more esophoria or exophoria at distance or near will be excluded from the study.

NPC: NPC is a routine clinical measurement that assesses the ability of the eyes to converge and accommodate while viewing a near target.[14] NPC will be evaluated binocularly with the subject's habitual correction using a push-up technique. An accommodative target (20/30 near letter) on a fixation stick will be slowly moved closer towards the subject's central visual axis until the subject experiences constant diplopia. The distance from the bridge of the subject's nose to this point will be recorded as the break point. Subjects with a break point of 6 cm or higher will be excluded from the study.

Accommodative Function: Accommodative function (lead/lag), or the ability of the subject to focus when reading, will be measured with an autorefractor. The autorefractor is a non-contact instrument that measures refractive error. Subjects will wear their habitual contact lens correction. Accommodative response will be measured at two stimulus levels with each pair of contact lenses (habitual, single vision, and multifocal) (2.00 and 4.00 diopters) to determine how accurately the subject focuses on letter visual targets at various distances while corrected with different contact lenses.

Dry Eye Testing: Subjects who have significant signs of dry eye will be excluded from the study. Basic dry eye testing, similar to that performed during a regular eye exam, will be performed to ensure subjects with dry eye do not confound study results. Tear break-up time (TBUT), ocular surface staining, and Schirmer test will be performed at the baseline examination. All dry eye tests will be performed on the right eye only.

TBUT: TBUT measurements are commonly used to assess severity of dry eye. The measurement quantifies the time it takes for the tear film to break-up on the ocular surface after a complete blink. To measure TBUT, fluorescein sodium will be instilled in the inferior palpebral conjunctiva using with a Barnes-Hind Ful-Glo Fluorescein Sodium Ophthalmic Strip that has been wetted with a drop of non-preserved saline. After instillation, the subject will be placed in a slit lamp and

instructed to blink several times. After several blinks, the subject will be asked to hold the blink for as long as possible. While the patient is holding the blink, the tear film will be observed through the slit lamp with cobalt blue light and a yellow barrier filter (Wratten 12 filter) held over the slit lamp objective to improve fluorescein visibility. The time of the first apparent tear break up will be recorded. Subjects with TBUT times of 7 seconds or lower will be excluded from the study.

Ocular Surface Staining: Fluorescein sodium is commonly used to assess corneal and conjunctival surface integrity and causes little to no ocular discomfort upon instillation. In the presence of ocular surface disruption, fluorescein glow will be easily observed with cobalt blue light. To assess ocular surface staining, fluoresce in previously used to assess TBUT will be sufficient. The subject will remain in the slit lamp and cobalt blue light will be used to assess severity of ocular surface staining. The Oxford Scheme[12] will be used to grade surface staining severity. Subjects with Grade 1 or higher ocular surface staining on either eye will be excluded from the study.

Schirmer Test: The Schirmer test is a standardized method used to measure tear flow and assess dry eye. It measures the tear flow using a filter paper that is inserted into the conjunctival sac. To perform this test, a Schirmer filter paper (5x35 mm Whitman No 1) will be placed on the lower lid, midway between the middle and outer third of the lid. The tip of the Schirmer paper will be tucked under the lid. The patient will be instructed to close his/her eyes for five minutes. After five minutes, the Schirmer paper will be removed and the tear flow measured on the filter paper will be recorded. Subjects with a Schirmer score of 7 mm or lower will be excluded from the study.

Keratograph 5M Measurements: The Keratograph 5M is a clinical instrument used to assess corneal curvatures and the tear film. This instrument is routinely used in clinical eye care and takes all measurements without touching the eye. For this study, the Keratograph 5M will be used to measure non-invasive TBUT over contact lenses, tear film meniscus height and eye redness after the subjects have worn their habitual contact lenses and the two lenses dispensed during the study. All Keratograph 5M measurements will be performed on the right eye only.

Subjective Refractive Error Determination: Subjects who meet all inclusion criteria for the study will be enrolled and be fitted in two different kinds of contact lenses throughout the course of the study. Before fitting the contact lenses, a subjective refraction will be performed to determine the best correction and contact lens power for the subject. The refraction will be performed by a licensed, trained optometrist (Dr. Rueff) using a phoropter. Patient responses will be used to determine the final refractive error. This method is identical to refractive error determination in a regular eye exam.

Contact Lens Fitting: In this crossover trial, single vision Bausch + Lomb ULTRA® contact lenses and Bausch + Lomb ULTRA® for Presbyopia contact lenses will be fitted by a licensed optometrist. Bausch + Lomb ULTRA® and Bausch + Lomb ULTRA® for Presbyopia are FDA-approved daily wear soft contact lenses. All subjects will be habitual soft contact lens wearers, so no increased risk will be assumed by fitting the Bausch + Lomb ULTRA® contact lenses.

Anterior Ocular Segment Assessment: While the risk of contact lens complications (ocular inflammation, infection, etc.) in this study is extremely low, the anterior segment ocular health of both eyes of every subject will be assessed by a licensed optometrist at each visit to ensure no complications have occurred. This assessment will also include the ocular adnexa (lid margin and Meibomian glands). In the unlikely event that a complication does occur, the subject will be treated by a licensed optometrist and dismissed from the study.

c. Detailed Study Procedures

Overview

This randomized, prospective, crossover clinical trial will recruit uncomfortable, single vision, soft contact lens wearers in the non-presbyopic age range. The tenants of the Declaration of Helsinki will be followed. Complete inclusion criteria are listed in Table 1. Each subject will receive a single vision (Bausch + Lomb ULTRA®) and multifocal contact lens (Bausch + Lomb ULTRA® for Presbyopia) to wear for 2 weeks each. Subjects will be masked and randomly assigned to the first lens and then they will be crossed over to the remaining lens for the second 2-week period. Figure 1 displays a flow chart of the planned study procedures.

Subject Enrollment and Baseline Examination and Fitting

Pre-presbyopes with symptoms of contact lens discomfort and asthenopia will be recruited from The Ohio State University College of Optometry Clinics. Interested subjects will be instructed to contact investigators by email. The Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8), a survey validated to reflect change in opinion of contact lenses,[11] will be administered over the phone to ensure each subject has significant discomfort symptoms. Each subject must have a score of ≥12 points[15] to qualify for the first, baseline examination.

At the baseline examination, inclusion criteria will be confirmed. The presence of concurrent dry eye or a binocular vision disorder (a group of disorders that involved how the eyes move together) will confound study results, so subjects with significant signs of these conditions will be excluded from the study (as defined in Table 1). With the each subject's habitual contact lens correction, heterophoria at distance and near and NPC will be measured to determine binocular vision eligibility. Accommodative function will also be assessed at this time. TBUT, ocular surface staining, and Schirmer testing will be performed to determine dry eye eligibility. Keratograph 5M tear imaging will also be performed at this time. A general anterior segment assessment will be made and assessment of the lid margins and Meibomian glands after habitual lens wear will be recorded. The CISS will be administered at the baseline examination. Subjects who meet all inclusion criteria will be enrolled and randomized (blocked randomization design with a 1:1 allocation ratio) to receive either the single vision Bausch + Lomb ULTRA® or single vision Bausch + Lomb ULTRA® for Presbyopia contact lenses first. All subjects who complete the baseline examination (whether enrolled or not) will receive $40 cash and a parking pass.

Each lens is made in only one size (base curve and diameter), so the main parameter determined during the fitting process will be power of the lens. For the single vision lens and multifocal lens, the power will be determine based on the spherical equivalent of the subject's refractive error. For the multifocal contact lens, subjects will receive a Low Add power in both eyes. Vision, fit, and comfort of the contact lens will be assessed in office on both eyes. Lenses will be allowed to settle on the eye for approximately 10 minutes before vision or fit are assessed. Once a satisfactory fit and visual end-point has been achieved (patient is comfortable in lenses, binocular vision is better than 20/40, and examiner determines proper contact lens fit), the subject will be instructed to wear the lenses daily for the next 2 weeks. Accommodative testing and heterophoria measurements with the first dispensed lens pair will be performed. Subjects will be instructed not to sleep in the contact lenses and to remove them each night to clean and soak and Biotrue ® contact lens solution. A clean contact lens case and Biotrue ® solution will be provided to each subject. Subjects will be given the contact information of the PI and instructed to contact investigators if they experience any signs of complications (redness, discharge, irritation, pain, etc.). Before leaving the baseline examination, each subject will schedule an appointment for the second examination approximately 2 weeks from the initial baseline examination date (no sooner than 2 weeks, no later than 3 weeks). The Bausch + Lomb ULTRA ® contact lenses are FDA-approved for daily wear. Subjects will receive $40 cash and a parking pass at the end of the baseline examination.

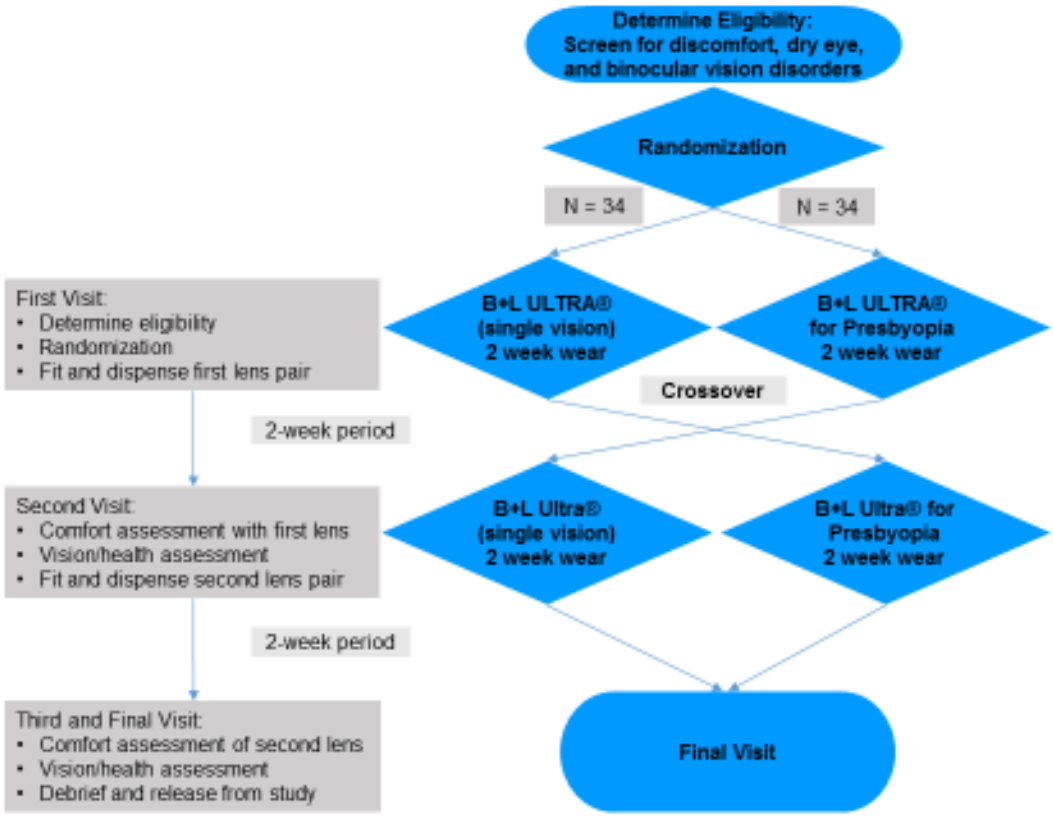

Figure 1: Flow chart of study procedures for randomized crossover clinical trial (Please see Data Analysis and Sample Size Justification section for updated sample size numbers)

Second Examination and Fitting

After wearing the first dispensed lens pair for approximately 2 weeks, subjects will return to the clinic. The CLDEQ-8 and CISS will be administered and subjects will be instructed to answer based on their experience with the first dispensed lens pair. Accommodative testing and heterophoria measurements with the first dispensed lens pair will be performed. The lenses will be removed, discarded, and an anterior ocular segment assessment will be performed on both eyes. An assessment of the lid margins and Meibomian glands will be performed. As well, an assessment of the tear film (TBUT, Schirmer test, and ocular surface staining) and tear film assessment with the Keratograph 5M will be performed.

Next, the remaining contact lens (Bausch + Lomb ULTRA® or Bausch + Lomb ULTRA® for Presbyopia, depending on which lens the subject wore first) will be fitted on each subject. Fit, vision, and comfort will be assessed (as in the baseline examination) after the lenses have settled on the eye for 10 minutes. When a satisfactory endpoint is reached, subjects will again be educated on proper lens care (daily lens wear, no sleeping in lenses, proper cleaning/storage with Biotrue® solution) and be given a fresh contact lens case and Biotrue® contact lens solution. Accommodative testing and heterophoria measurements with the second dispensed lens pair will be performed. Each subject will schedule an appointment for the third and final examination approximately 2 weeks from the date of the second examination. Subjects will receive $40 cash and a parking pass at the end of the second examination.

Third and Final Examination

After wearing the second dispensed lens pair for approximately 2 weeks, subjects will return to the clinic. The CLDEQ-8 and CISS will be administered and subjects will be instructed to answer based on their experience with the second dispensed lens pair. Accommodative testing and heterophoria measurements with the second dispensed lens pair will be performed. The lenses will be removed, discarded, and an anterior ocular segment assessment will be performed on both eyes. An assessment of the lid margins and Meibomian glands will be performed. As well, an assessment of the tear film (TBUT, Schirmer test, and ocular surface staining) and tear film assessment with the Keratograph 5M will be performed.

Subjects will be asked which of the two trial lens pairs they preferred and be asked which lens (single vision or multifocal) they think they had first and second. After all testing and procedures have been completed, subjects will be instructed to return to habitual contact lens wear and informed of what lenses they had during the first and second trial periods. Subjects will receive $40 cash and a parking pass at the end of the third examination.

Data Analysis and Sample Size Justification

Paired *t* tests will be performed to compare mean CLDEQ-8 scores with habitual single vision lenses, single vision Bausch + Lomb ULTRA® contact lenses, or Bausch + Lomb ULTRA® for Presbyopia contact lenses to one another. Repeated measures ANOVA testing will be performed to determine if contact lens comfort (CLDEQ-8 score) is affected by age or magnitude of myopia when subjects are corrected with their habitual single vision lenses, single vision Bausch + Lomb ULTRA® contact lenses, or ULTRA® for Presbyopia contact lenses. CISS scores throughout the trial will be analyzed in the same way as the CLDEQ-8 scores. To determine if accommodative ability is related to multifocal preference, paired *t* tests will be used to compare contact lens preference (single vision versus multifocal) to initial accommodative function (lag/lead) values.

In order to detect a conservative standardized effect size of 0.6 ($\alpha = 0.05$, $\beta = 0.20$), a sample size of 45 subjects would be necessary. A previous cross-over trial utilizing the CLDEQ-8 reported a 20% loss-to-follow-up rate.[11] Anticipating and accounting for a similar rate in our subject enrollment, a sample of 54 subjects would be appropriate. Because the hypotheses of this study have never been tested, we recognize that this initial sample size may seem inadequate after all data is collected. So, our initial 54-subject sample size will be increased by an additional 25% to allow for additional data collection that may be necessary. Therefore, 68 subjects (34 subjects per group) will be sought for IRB approval to account for the possibility of needing more subject data to make reliable study conclusions.

Updated sample size (03/07/2017): At this point in the study, we have seen 26 total subjects: 17 were successfully enrolled and 9 failed to qualify for the study (did not meet all dry eye and binocular vision inclusion criteria) after completing the baseline examination. Therefore, approximately 35% of the subjects who have participated in baseline examinations have failed. With 17 subjects enrolled, we need to recruit and enroll an additional 51 subjects to complete the study. Considering our recent experience with enrollment, we will assume that 35% of these 51 baseline examinations (or about 18) will not qualify for the study. Therefore, we are requesting to increase our original sample size of 68 subjects by 18 and recruit a sample size of 86 (43 subjects per group).

Updated sample size (8/14/2017): Upon initial data analysis of the subjects who have completed the study, we found an interaction between subject age group and change in CLDEQ-8 survey score that, while not statistically significant ($p = 0.12$), was clinically significant (an approximate 4-point difference between age groups) according to CLDEQ-8 interpretation. We have hypothesized that this clinically relevant finding may have lacked statistical significance because of an inadequate sample size. Because of the lack of software or well-developed methods for calculating the sample size for an interaction in a cross-over study, a simulation study was conducted to estimate what a sufficient sample size would be. The simulation assessed adding more subjects to the sample – using

the subjects currently in the sample. This iterative process was conducted to draw 10 different samples from which sample size was estimated in order to attempt to replicate the original finding with greater power. Given the simulation, it was recommended that 30 additional subjects be tested. At this point, approximately 27% of subjects who present for the baseline examination fail to qualify for the study, so we will increase the 30 additional subjects by 27% (8 subjects) and, therefore, increase our overall sample size by 38 subjects. In conclusion, the new number of recruited participants will increased from 86 to 124.

Updated Sample Size (11/21/2017): At this stage in the study, we have successfully enrolled 69 subjects, and 35 subjects have failed to qualify for the study after completing the baseline examination. In total, we have recruited 104 of the 124 approved subjects for this study. The 27% baseline examination failure rate we observed during the first recruitment stage has increased to 66%. Specifically, since beginning this new round of recruitment, we have enrolled 15 subjects in the study and had 15 baseline examination failures (making our total recruitment at 104 subjects). In order to enroll the 30 additional subjects described above (on 8/14/2017) and allow for anticipated baseline examination failures, we will increase the number of recruited participants from 124 to 144.

Timeline

We anticipate that the data collection portion of this project will take 6 to 7 months to complete. At the time of this protocol submission, we can anticipate that IRB approval and all other contractual agreements will be finalized and approved by mid-December 2016. At this time, we will aggressively start recruitment by advertising in the OSU College of Optometry, OSU Medical and OSU Main Campuses. We will also send postcards to OSU College of Optometry Contact Lens Clinic patients.

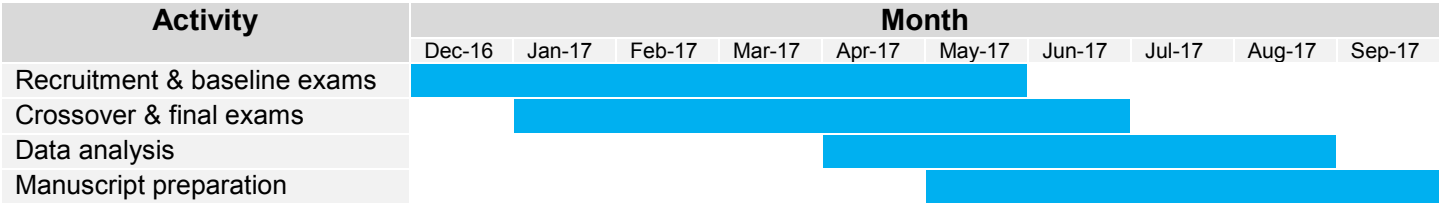

Table 2: Timeline of study activities

We expect that recruitment and enrollment of all 54 subjects will take 5 to 6 months (ending in May 2017). This estimate accounts for slower anticipated recruitment (5-10 subjects per month) in December due to the holidays. Recruitment rates starting in January 2017 are anticipated to be higher (10-15 subjects per month). Dr. Rueff will be spending approximately 30 hours per week recruiting subjects and performing examinations and organizational study tasks during the data collection portion of the study. If we estimate that each subject will require approximately 5 hours of total examination time throughout the course of the entire study, she will have sufficient time budgeted to complete all recruitment and data collection. All data collection is projected to be complete before July 2017. Table 2 shows a projected timeline of study activities.

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