Examination of Myopia Progression and Consequences and Mechanisms of Soft Multifocal Contact Lens Control

National Clinical Trial (NCT) Identified Number: NCT04080128

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
9.2	Updated with calculations for loss-to-follow-up	To have a complete picture of what power the analyses will have under various scenarios.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Examination of Myopia Progression and the Consequences and Mechanisms of Soft Multifocal Contact Lens Myopia Control

Study Description: Establishing a treatment that slows the progression of myopia is the first step in the process of potentially preventing myopia onset. The BLINK2 Study will provide significant myopia control information, including additional knowledge about the mechanism of eye growth regulation that will aid optimization of treatments that may ultimately slow or prevent myopic eye growth. However, myopic eye growth is not linear, and it does not have a consistent period of development. It is therefore difficult to know whether individuals are likely to progress. If we can determine the patients who are most likely to progress, we can provide specifically them with myopia control treatment, which will optimize benefit while minimizing risk.

Objectives: Primary Outcomes: The specific aims to be conducted on the BLINK2 Study participants are to:

1. test the hypothesis that thinner subfoveal choroidal thickness is associated with greater axial elongation,

2. test the hypothesis that less ipRGC activity (as measured by blue light-driven inputs to the pupil response) is associated with greater axial elongation, and
3. test the hypothesis that exposure to lower light levels is associated with greater axial elongation.
4. test the hypothesis that long-term soft multifocal contact lens wear does not alter accommodative amplitude, lag of accommodation, or accommodative facility. This hypothesis predicts that at the baseline BLINK2 Study visit, these accommodative measures will be similar across the three treatment groups that were randomly assigned at the beginning of the BLINK Study; if they are not similar, they will become similar over the next two years.
5. test the hypothesis that soft multifocal contact lenses slow rather than merely delay myopia progression. This hypothesis predicts that during the first two years of the BLINK2 Study, when all participants will wear soft multifocal contact lenses, participants will progress at the same rate regardless of original lens assignment in the BLINK Study. Alternatively, faster myopia progression in participants originally fitted with soft multifocal contact lenses compared to single vision contact lenses would indicate a delay in myopia progression rather than a permanent treatment benefit.
6. test the hypothesis that there is no increase in myopia when switching from multifocal to single vision contact lenses. This hypothesis predicts that the progression of myopia during the last year of follow-up (all participants will switch to single vision contact lenses), will be similar to myopia progression during the first two years (all participants wore multifocal contact lenses). Alternatively, faster progression after switching to single vision contact lens wear indicates a “rebound” of myopia progression.

Endpoints:

Primary Endpoints:
1. The statistical correlation between choroidal thickness and axial length over three years.
2. The statistical correlation between iPRGC activity and axial length over three years.
3. The statistical correlation between light levels and axial length over three years.

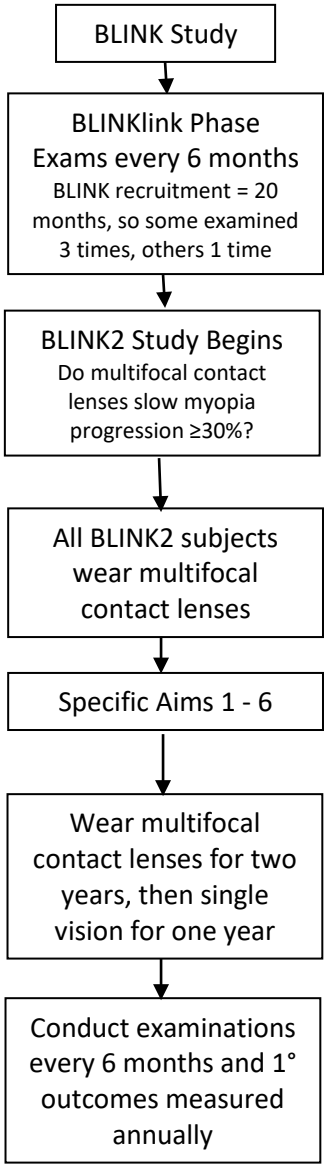
Secondary Endpoints:

	4. The accommodative amplitude, accommodative lag, and the accommodative facility will be comparable among the three treatment groups at the onset of BLINK2. 5. Myopia progression over the two years following fitting all participants with soft multifocal contact lenses, and following them for two years. 6. Myopia progression after switching participants back into single vision contact lenses at the beginning of the third year of follow-up.
Study Population:	There are 247 participants in BLINK2, about 84% of the original 293 participants.
Phase:	N/A[1].
Description of Sites/Facilities Enrolling Participants:	Participants are enrolled at The Ohio State University College of Optometry, Columbus, OH, and the University of Houston College of Optometry.
Description of Study Intervention:	All participants will be switched into the multifocal lenses for years 1 and 2 of BLINK2. In year 3, participants will then be switched in the single vision contact lenses to evaluate any potential rebound effect.
Study Duration:	60 months
Participant Duration:	36 months

1.2 SCHEMA

[1] From 21 CFR 312.21 "Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects… Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects."

Flowchart illustrating the subject flow from the BLINK Study to the BLINKlink Phase and finally to the BLINK2 Study.



1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1 Visit numbers and timing of the visit.

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

Procedures performed at each visit are noted in Table 2. All measures will be performed by an Examiner because all participants will receive the same treatment.

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

	Baseline and Annual Visits 1, 4, 6, 9	1 Week CL Check Visits 2 and 7	Semiannual Visits Visits 3, 5, 8
High contrast VA with CL (OU)	X		X
Low contrast visual acuity with CL (OU)	X		X
Near visual acuity with CL (OU)	X		X
Modified Thorington	X		
Accommodative lag (OD)	X		
Accommodative amplitude (OD)	X		
Accommodative facility (OU)	X		
Pupil size (OD)	X		

Slit lamp examination (OU)	X	X	X
Contact lens centration (OU)	X	X	X
Choroidal thickness (OD)	X		
ipRGC pupil protocol (OD)	X		X
Non-cycloplegic autorefraction			X
Non-cycloplegic axial length			X
Activity watch training	X		X
Cycloplegic autorefraction (OU)*	X		
Axial length (OU)*	X		
Peripheral axial length (OD)*	Visits 6 & 9		
Dilated fundus examination (OU)*	X		
Contact Lens Survey	X		X
PREP2 survey	X		X
CISS survey of visual function	X		
Compliance survey	X		X
Length of visit (hours)	2.0	0.5	0.75

* = cycloplegic

2 INTRODUCTION

2.1 STUDY RATIONALE

The BLINK2 Study is a continuation of the BLINK Study. This investigation will provide important, previously unmet answers regarding biological associations with myopia progression in order to better predict the patients most likely to benefit from myopia control, as well as questions frequently posed by patients and practitioners about the side effects, mechanism, and discontinuation of soft multifocal contact lens myopia control. The first three aims examine the association between biological variables that can be measured non-invasively and myopia progression. The last three specific aims are being conducted because soft multifocal contact lenses slow myopia progression by 30% or more, and they can be investigated with very few additional measurements.

2.2 BACKGROUND

Myopia currently affects one-out-of-every-three people in the United States, and it is projected to affect half of the world's population by 2050.[1] It is the second most common cause of blindness and leading cause of visual impairment globally.[2] High myopia enhances the risk of sight-threatening complications such as cataract, glaucoma, choroidal atrophy, retinal detachment, and myopic macular degeneration,[3-6] but people with less than 5.00 D of myopia are still at risk, and low myopia is far more prevalent than high myopia. Ultimately, 43% of myopic retinopathy is experienced by patients with less than 5.00 D myopia.[7] Although a direct link between slowed myopia progression and a decrease in myopia-related sight-threatening complications has never been established, retinal stretching is a plausible scientific explanation that lends credence to the theory that myopia control would decrease morbidity.[8] Lower myopic refractive error also results in improved uncorrected visual acuity,[9, 10] which ultimately leads to better quality of life,[11, 12] and refractive surgery results are also more predictable for participants with lower myopia.[13] Myopia control could therefore positively affect the lives of millions of people world-wide.

Furthermore, the National Eye Institute recognizes the importance of regulating myopic eye growth in order to decrease the burden of the disease on society. The latest draft of the National Eye Institute's *Vision Research: Needs, Gaps, and Opportunities (www.nei.nih.gov/strategicplanning)* states the need to "evaluate the efficacy of potential treatments for delaying the onset or for slowing the progression of myopia, such as lenses that alter peripheral defocus, pharmaceutical approaches, or behavioral methods that harness the beneficial effects of more time outdoors."

Establishing a treatment that slows the progression of myopia is the first step in the process of potentially preventing myopia onset. The BLINK2 Study will provide significant myopia control information, including additional knowledge about the mechanism of eye growth regulation that will aid optimization of treatments that may ultimately slow or prevent myopic eye growth. However, myopic eye growth is not linear,[14-17] and it does not have a consistent period of development.[18-20] It is therefore difficult to know whether individuals are likely to progress. If we can determine the patients who are most likely to progress, we can provide specifically them with myopia control treatment, which will optimize benefit while minimizing risk.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks are minimal. There is no reasonable risk of physical harm from the non-contact recording of eye images used in this study. However, participants may become bored or frustrated with the need to keep the eyes still and fixating on targets during the measurement procedures. A participant and his or her parents may feel inconvenienced by being asked to devote time and/or travel to the clinical site. Participants' pupils will be dilated at the baseline visit and each annual examination. As a result of being dilated, participants will be light sensitive and their near vision will be blurry. Participants will be given

disposable sunglasses to alleviate light sensitivity and they can remove their correction to see clearly at near during cycloplegia. Daily wear soft contact lenses have a corneal ulcer rate of approximately 1/2000 per participant-year.[21]

Other problems that can occur with contact lens wear include: burning, stinging, and/or itching of the eyes; less comfort after all day wear; foreign body sensation; inflammation of the cornea and/or scratch of the cornea; swelling of the cornea, neovascularization; corneal staining; redness, tarsal abnormalities; iritis, excessive watering, unusual eye secretions, or redness of the eye; blurred vision, rainbows or halos around objects; sensitivity to light; and dry eyes. Though unlikely, there is the possibility of skin irritation (e.g., rash) when wearing a watch band. This risk is no greater than when wearing any other wrist-worn watch.

2.3.2 KNOWN POTENTIAL BENEFITS

All participants will receive free comprehensive eye care, discounted glasses, and free contact lenses and contact lens supplies (as applicable) 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.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks appear to be small in relation to the potential benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To test the hypothesis that thinner subfoveal choroidal thickness is associated with greater axial elongation	The statistical correlation between choroidal thickness and axial length over three years.	Choroidal thickness has been associated with myopia, but there is a lack of data over time evaluating the relationship.
To test the hypothesis that less ipRGC activity (as measured by blue light-driven inputs to the pupil response) is associated with greater axial elongation	The statistical correlation between iPRGC activity and axial length over three years.	Dopamine levels, as inferred from ipRGC activity, have been posited to be associated with progression, but no long-term data exist.
To test the hypothesis that exposure to lower light levels is associated with greater axial elongation.	The statistical correlation between light levels and axial length over three years.	The effect of light may be independent of dopamine, and rather associated with

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		amount of light exposure.
Secondary		
To test the hypothesis that long-term soft multifocal contact lens wear does not alter accommodative amplitude, lag of accommodation, or accommodative facility. This hypothesis predicts that at the baseline BLINK2 Study visit, these accommodative measures will be similar across the three treatment groups that were randomly assigned at the beginning of the BLINK Study; if they are not similar, they will become similar over the next two years.	The accommodative amplitude, accommodative lag, and the accommodative facility will be comparable among the three treatment groups at the onset of BLINK2.	The effect of the application of multifocal lenses on the accommodative abilities of children has been questioned. Amplitude, facility, and lag comparisons will address whether these abilities have been affected.
To test the hypothesis that soft multifocal contact lenses slow rather than merely delay myopia progression. This hypothesis predicts that during the first two years of the BLINK2 Study, when all participants will wear soft multifocal contact lenses, participants will progress at the same rate regardless of original lens assignment in the BLINK Study. Alternatively, faster myopia progression in participants originally fitted with soft multifocal contact lenses compared to single vision contact lenses would indicate a delay in myopia progression rather than a permanent treatment benefit.	Myopia progression over the two years following fitting all participants with soft multifocal contact lenses, and following them for two years.	Spherical equivalent as the measure of myopia will answer whether or not there is a delay or actual slowing of myopia progression.
We will test the hypothesis that there is no increase in myopia when switching from multifocal to single vision contact lenses. This hypothesis predicts that the progression of myopia during the	Myopia progression after switching participants back into single vision contact lenses at the beginning of the third year of follow-up.	Spherical equivalent will be used to define whether there is an increase in myopia progression after discontinuation.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
last year of follow-up (all participants will switch to single vision contact lenses), will be similar to myopia progression during the first two years (all participants wore multifocal contact lenses). Alternatively, faster progression after switching to single vision contact lens wear indicates a “rebound” of myopia progression.		

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a longitudinal cohort study that is being conducted at two US locations. Participants will wear soft multifocal contact lenses.

This investigation will provide important, previously unmet answers regarding biological associations with myopia progression in order to better predict the patients most likely to benefit from myopia control, as well as questions frequently posed by patients and practitioners about the side effects, mechanism, and discontinuation of soft multifocal contact lens myopia control. The first three aims examine the association between biological variables that can be measured non-invasively and myopia progression. The last three specific aims will look at the differences resulting from the treatment effect, and they can be investigated with very few additional measurements.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is a continuation of a clinical trial as an observational cohort. The findings of the BLINK Study determined that participants will be wearing multifocal contact lenses for the first two years of the study.

4.3 JUSTIFICATION FOR DOSE

The type of contact lenses used during the first two years of the study were determined by the findings of the BLINK Study.

4.4 END OF STUDY DEFINITION

The BLINK2 Study will be considered complete for a participant when he/she has had their three-year visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form (Parental Permission and Assent)
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Completed participation in the BLINK Study

5.2 EXCLUSION CRITERIA

There are no exclusion criteria.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

N/A

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Retention is very important for longitudinal studies, in order to reduce the potential for bias and to maintain adequate statistical power to answer each of the specific aims. Participants will receive free comprehensive eye care, free contact lenses and solutions, and discounted glasses during the BLINK2 Study.

We continue to send monthly emails to participants' parents, each one with a different message of contact lens compliance and to maintain contact between visits. During their current visit, an appointment is made for the following visit (or two visits if they include a one-week contact lens check). The appointments are set for the beginning of the visit window, so that they can be rescheduled within the visit window if necessary. Reminder calls or emails are used a couple of weeks in advance of the visit to confirm or reschedule the appointment as needed. A reminder call is also made the day before the appointment.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Multifocal and spherical study contact lens descriptions
BIOFINITY (comfilcon A) Contact Lenses are available as spheric, aspheric, toric and multifocal lens designs. The lenses are made from a material containing 48% water and 52% comfilcon A, a silicone-containing hydrogel. The lenses have a tint (phthalocyanine blue) which is added to make the lens more visible for handling.
BIOFINITY MULTIFOCAL and **BIOFINITY XR MULTIFOCAL** contact lenses parameters:
o Diameter: 13.5 mm to 15.0 mm
o Base Curve: 8.0 mm to 9.5 mm
o Center Thickness: 0.08 mm to 0.60 mm (varies with power)
o Powers: -20.00 D to +20.0 D
o Addition Powers: +0.50 D to +3.00 D
The physical/optical properties of the lens are:
o Refractive Index: 1.40
o Light Transmittance: >97%
o Surface Character Hydrophilic
o Water Content 48%
o Specific Gravity 1.04
o Oxygen Permeability: 128 x 10-11 (cm2/sec)(ml 02/ml x mmHg) 35°C (Coulometric method)

If unable to wear the study contact lenses, these lenses are prescribed.

PROCLEAR MULTIFOCAL contact lenses parameters:
o Diameter: 14.4mm
o Base Curve: 8.70
o Center Thickness: 0.15 to 0.35 mm (varies with power)
o Powers: +4.00 to -6.00 D in 0.25 D steps
o Addition Powers: +1.00, +1.50, +2.00, or +2.50 D

PROCLEAR MULTIFOCAL XR contact lenses parameters:
o Diameter: 14.4mm
o Base Curve: 8.4, 8.70
o Center Thickness: 0.15 to 0.35 mm (varies with power)
o Powers: +20.00 to -20.00 D in (0.50 D steps after +/- 6.50 D)
o Addition Powers: +1.00, +1.50, +2.00, +2.50, +3.00, +3.50, or +4.00 D

The physical/optical properties of the lenses are:
o Refractive Index: 1.387
o Light Transmittance: >90%
o Surface Character Hydrophilic
o Water Content 62%
o Specific Gravity 1.76

Oxygen Permeability Guard Ring Edge Corrected 27 x 10-11
Boundary Layer Corrected**34 x 10-11
*(cm_2/sec) (ml O_2/ml x mm Hg) at 35° C. as measured by 201T Permeometer connected to a curved Rehder guard ring polarographic cell.

6.1.2 DOSING AND ADMINISTRATION

Contact lenses are worn daily. If the spherical contact lenses are the modality, they are disposed of daily. If the multifocal contact lenses are the modality, the care regimen will be followed and the lenses will be disposed of monthly.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The study contact lenses are ordered from the manufacturer and arrive as they would at any physician's office. The study lenses are stored in a locked cabinet behind a locked door. The contact lens inventory is maintained by the Clinic Coordinator at each site. The lenses are dispensed to participants by either the examiner or a coordinator. Participants are reminded to check expiration dates of any lenses at home and to discard these. Because all lenses are post market and known to the participant we will not require that unused product be returned.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The lenses to be used are dependent on the results of the BLINK Study. During the first two years participants will wear either Biofinity Multifocal contact lenses or MyDay daily disposable lenses, both manufactured by CooperVision. All participants will wear the MyDay daily disposable lenses during the third year. Because participants will be unmasked to the type of correction being worn contact lenses will be dispensed in their original blister packs. Each lens is supplied sterile in a blister pack containing buffered isotonic saline solution. The blister is labeled with the base curve, diameter, dioptric power, manufacturing lot number, and expiration date of the lens.

6.2.3 PRODUCT STORAGE AND STABILITY

The study lenses should not be used if the blister pack is broken or the seal has been damaged. Otherwise, there are no specific storage requirements for these lenses.

6.2.4 PREPARATION

No preparation of the contact lenses will be needed. They will be dispensed as received from the manufacturer. Instructions on insertion and removal of the lenses will be provided to participants.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

While the BLINK Study was masked, the BLINK2 Study will be an unmasked study. There will be no randomization as all participants will wear the same lenses during the study.

6.4 STUDY INTERVENTION COMPLIANCE

All participants will complete a compliance survey at visits 1, 3, 4, 5, 6, 8, and 9 (annual and semiannual visits) in order to determine how compliance with contact lens wear may affect myopia control. Parents will also complete a compliance survey at these same visits. These surveys ask how often the lenses are being worn (how many days during the week and on the weekend), and for how many hours a day.

Proper procedures for contact lens care are reviewed at each appointment.

6.5 CONCOMITANT THERAPY

This section is not applicable.

6.5.1 RESCUE MEDICINE

This section is not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from contact lens wear does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Participants may be advised to temporarily discontinue contact lens wear for Adverse Events, based on the clinician's assessment on an individual basis. Participants will have follow ups either via phone or in person, depending on the clinician's diagnosis.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. If a participant wishes to discontinue and all alternatives have been discussed, the examiner should ask the participant if he or she would come back for visit 9 only. Examiners will maintain participants in the study regardless of compliance. If a participant withdraws from the study the Study Discontinuation Form will be completed.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the final study visit and is unable to be contacted by the study site staff. If a participant moves from the clinic area, the participant may be examined at the other clinic site or the clinic may pay for the participant and one adult (if

participant is younger than 18 years) to fly to an appointment, one night's stay in a hotel, and ground transportation. If the participant is 18 years or older, then we will offer payment for the participant only.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit when the participant is late arriving for the appointment.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.] This determination will not be made until the end of the study in case the participant/parent will agree to return for the final study visit.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The following testing will be performed.

- **Administration of surveys**: PREP2, Subject Contact Lens Survey, CISS, and Parent Compliance Survey
- **Procedures that will be completed during the study as part of regular standard of clinical care**: For medicolegal reasons we will perform slit lamp biomicroscopy, contact lens fitting assessment, and dilated fundus exam
- **Research Procedures:** Visual Acuity measures, Modified Thorington, accommodative lag, amplitude and facility, pupil size, choroidal thickness measurements, ipRCG, light exposure via an Actiwatch, autorefraction, axial length

8.2 SAFETY AND OTHER ASSESSMENTS

For medicolegal reasons we will perform slit lamp biomicroscopy, contact lens fitting assessment, visual acuity, and dilated fundus exam.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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. 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.

A serious adverse event is any adverse event that is fatal or life threatening, is permanently disabling (two line or more loss of best-corrected visual acuity), requires participant hospitalization or prolongs hospitalization, or results in a congenital anomaly or birth defect.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines are used to describe 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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In this study relationship to study lenses will be noted using the following scale.

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.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Examiners will note whether the AE is considered expected or unexpected using the following scale.
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 participant population
2. related or possibly related to participation in the research
3. suggests that the research places participants or others at a greater risk of harm than was previously known or recognized

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

1. The participant experiences/presents with ocular signs or symptoms worse than those encountered during routine contact lens wear (e.g., a slit lamp sign of ≥ Grade 3). It is up to the Examiner to determine when an Adverse Event Form should be completed.

2. At every visit, the Examiner must ask the participant'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 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 Examiner, after asking appropriate follow-up questions.

   For example, if a parent says that her child had a headache, the 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 Examiner believes that it may be related to the study treatment, then an Adverse Event Form should be completed.

3. The Examiner should ask the parent/participant 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 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 Examiner is unsure of whether or not something should be categorized as an adverse event, an Adverse Event form should be completed.

The 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 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.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Clinic Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

8.3.5 ADVERSE EVENT REPORTING

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. 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.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The examiner will immediately report to the site PI any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The site PI will immediately contact the Study Chair's office and the DCC. The National Eye Institute, the DMOC, and the IRB of record will be contacted within 24 hours of the occurrence.

All serious adverse events will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the DCC and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Treatments used in this study consist of routine myopia management strategies, so we don't anticipate informing participants about AEs or SAEs on an individual or aggregate level. Should the need arise, the Executive Committee, in consultation with the DMOC, will determine the best method of informing participants.

8.3.8 EVENTS OF SPECIAL INTEREST

This section is not applicable.

8.3.9 REPORTING OF PREGNANCY

Participant pregnancy would be documented as an Adverse Event in this study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Should an unanticipated problem arise, the Executive Committee, in consultation with the NEI and the DMOC, will discuss and implement changes to address the problem going forward.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for

Human Research Protections (OHRP) within 14 days of the IRB's receipt of the report of the problem from the investigator.]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Should the need arise, the Executive Committee, in consultation with the DMOC, will determine the best method of informing participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

1. The statistical correlation between choroidal thickness and axial length [Time Frame: Three years]
   test the hypothesis that thinner subfoveal choroidal thickness (a layer of blood vessels) is associated with greater axial elongation (eye growth)
2. The statistical correlation between iPRGC activity and axial length [Time Frame: Three years]
   test the hypothesis that less ipRGC activity (cells in the back of the eye as measured by blue light-driven inputs to the pupil response) is associated with greater axial elongation (eye growth)
3. The statistical correlation between Light levels and axial length [Time Frame: Three years]
   test the hypothesis that exposure to lower light levels is associated with greater axial elongation (eye growth)

- Secondary Efficacy Endpoint(s):

1a. Accommodative amplitude [Time Frame: Two years]
We will test the hypothesis that long-term soft bifocal contact lens wear does not alter accommodative amplitude. This hypothesis predicts that at the baseline BLINK2 Study visit, the accommodative amplitude will be similar across the three treatment groups that were randomly assigned at the beginning of the BLINK Study; if they are not similar, they will become similar over the next two years.

1b. Lag of accommodation [Time Frame: Two years]
We will test the hypothesis that long-term soft bifocal contact lens wear does not alter accommodative lag. This hypothesis predicts that at the baseline BLINK2 Study visit, accommodative lag will be similar across the three treatment groups that were randomly assigned at the beginning of the BLINK Study; if they are not similar, they will become similar over the next two years.

1c. Accommodative facility [Time Frame: Two years]
We will test the hypothesis that long-term soft bifocal contact lens wear does not alter accommodative facility. This hypothesis predicts that at the baseline BLINK2 Study visit, the accommodative facility will be similar across the three treatment groups that were randomly

assigned at the beginning of the BLINK Study; if they are not similar, they will become similar over the next two years.

2. Slowing of myopia progression [Time Frame: Two years]
   We will test the hypothesis that soft bifocal contact lenses slow rather than merely delay myopia progression. This hypothesis predicts that during the first two years of the BLINK Study, when all participants will wear soft bifocal contact lenses, participants will progress at the same rate regardless of original lens assignment in the BLINK Study. Alternatively, faster myopia progression in participants originally fitted with soft bifocal contact lenses compared to single vision contact lenses would indicate a delay in myopia progression rather than a permanent treatment benefit.
3. Rebound of progression [Time Frame: One year]
   We will test the hypothesis that there is no increase in myopia when switching from bifocal to single vision contact lenses. This hypothesis predicts that the progression of myopia during the last year of follow-up when all participants will switch to single vision contact lenses, will be similar to myopia progression during the first two years when all participants wore bifocal contact lenses. Alternatively, faster progression after switching to single vision contact lens wear indicates a "rebound" of myopia progression.

9.2 SAMPLE SIZE DETERMINATION

All sample size calculations were performed using SAS 9.3 software using $\alpha = 0.05$ and $\beta = 0.10$ (power = 80%). Estimates of sample size were computed for each specific aim.

Power Analysis Aim 1

The goal of Aim 1 is to assess whether there exists relationships between rate of axial elongation and subfoveal choroidal thickness. For this aim we will quantify the relationships using repeated measures mixed regression. With a sample of 247, we will have 88% power to detect a relationship if the partial correlation of axial elongation rate and subfoveal choroidal thickness is at least 0.20. With 247, we will have 90% power if the partial correlation of axial elongation rate and a question predictor is at least 0.21. We also explored what impact loss to follow-up of 5% (resulting in n=234), 10% (resulting in n=222), and 15% (resulting in=209) has on effect size. Losses of 5%, 10%, and 15% result in treatment group sizes of about 78, 74, and 69, respectively. For samples of 234 or 222, we will have 90% power if the partial correlation of axial elongation rate and a question predictor is at least 0.22, and at least 0.23 for a sample of 209.

Power Analysis Aim 2

The goal of Aim 2 is to assess whether there exist relationships between rate of axial elongation and ipRGC activity. For this aim, we will quantify the relationships using repeated measures mixed regression. With a sample of 247, we will have 88% power to detect a relationship if the partial correlation of axial elongation rate and ipRGC activity is at least 0.20. With 247, we will have 90% power if the partial correlation of axial elongation rate and a question predictor is at least 0.21. We also

explored what impact loss to follow-up of 5% (resulting in n=234), 10% (resulting in n=222), and 15% (resulting in=209) has on effect size. Losses of 5%, 10%, and 15% result in treatment group sizes of about 78, 74, and 69, respectively. For samples of 234 or 222, we will have 90% power if the partial correlation of axial elongation rate and a question predictor is at least 0.22, and at least 0.23 for a sample of 209.

Power Analysis Aim 3

The goal of Aim 3 are to assess whether there exist relationships between rate of axial elongation and light levels. For this aim we will quantify the relationships using repeated measures mixed regression. With a sample of 247, we will have 88% power to detect a relationship if the partial correlation of axial elongation rate and a light levels is at least 0.20. With 247, we will have 90% power if the partial correlation of axial elongation rate and a question predictor is at least 0.21. We also explored what impact loss to follow-up of 5% (resulting in n=234), 10% (resulting in n=222), and 15% (resulting in=209) has on effect size. Losses of 5%, 10%, and 15% result in treatment group sizes of about 78, 74, and 69, respectively. For samples of 234 or 222, we will have 90% power if the partial correlation of axial elongation rate and a question predictor is at least 0.22, and at least 0.23 for a sample of 209.

Power Analysis Secondary Aim 1

Testing for Secondary Aim 1 will include 6 tests, two tests for each accommodative variable. To achieve a family–wise error rate of 0.05, we will use a Bonferroni correction. The power analyses below assumed an alpha level of 0.0083.

***Secondary Aim 1a*: Accommodative Amplitude -** For accommodative amplitude, we will assume a standard deviation of 1.63.[22] We will also assume that 1.5 D is a clinically meaningful effect size as well as an adequate limit for equivalence bounds. Given these assumptions, samples of 78 per group have at least 90% power to detect equivalence.

***Secondary Aim 1b:* Accommodative Lag -** For accommodative lag, Berntsen et al.[23] report a standard deviation of 0.63 D for 10.4 +/- 1.8 year old myopes. With equivalence bounds of [-0.5, 0.5], samples of 78 per group have at least 90% power to detect equivalence.

***Secondary Aim 1c*: Accommodative Facility -** For accommodative facility, we assume a standard deviation of 3.7 cycles per minute, the finding for 10-15 year old myopes by Gong et al.[24] Four cycles was the effect size observed by Allen et al.[25] after three days of training. For power analysis, rather than using 4 cycles per minute to set limits for clinically meaningful differences, we will assume the more conservative equivalence bound of [-3.7, 3.7] provided by the assumed standard deviation. Given these assumptions, samples of78 per group have at least 90% power to detect equivalence.

Power Analysis Secondary Aim 2

The goal of Secondary Aim 2 is to assess whether a relationship exists between rate of progression of spherical equivalent and treatment group. Two contrasts are of principal interest, the comparison of the +1.50D add group to the single vision CL group, and the comparison of the +2.50D add group to the single vision CL group. Given two tests, for the power analysis we used an alpha level of 0.025, which is

the Bonferroni correction for multiple testing. With 78 or 74 participants in each contrast group, we estimate that we will have 89% power to detect a between group slope difference of at least 0.15 D. To achieve at least 90% power, it is estimated that the slope difference will need to be at least 0.16 D. With samples of about 69 per group, we will have at least 90% power to detect a slope difference of at least 0.17 D.

To get the slope difference estimate we used the method described by Stroup.[26] The method begins with the creation of a data set with a structure similar to that which will eventually be used to analyze the study data. In the data set, expected responses appear in place of observed data. The data are analyzed using a model like that intended for the study data. The resulting F statistics provide the basis for power calculations.

In our application of the method, the CLEERE data were used to formulate the data set and estimate other parameters needed to fit a repeated measures mixed regression model. We increased the residual model error estimated by the CLEERE data by 50% to provide a more conservative power estimate Assuming a linear growth model for spherical equivalent as a function of time (for time points 0, 1, and 2), we iterated though a range of slope differences between two groups of 78 participants until we identified a difference that could be detected with 89% power. That difference was 0.16 D.

Power Analysis Secondary Aim 3

The goal of Secondary Aim 3 is to assess whether the slope of the mean growth trajectory of spherical equivalent changes in the final year of the study, when all study participants wear single vision contact lenses. With a sample size of 247 or 234, we estimate that we will have 90% power to detect a change in slope of at least 0.16 D. With total sample sizes of 222 or 209, it is estimated that we will have 90% power to detect a slope difference of at least 0.17 D.

As with Secondary Aim 2, to get the estimate we used CLEERE data to implement the power estimate strategy described by Stroup. Again, we increased the residual model error estimated by the CLEERE data by 50% to provide a more conservative power estimate Assuming a linear growth model for spherical equivalent as a function of time (with time points 0, 1, 2 and 3), we iterated though a range of slope changes between time points 2 and 3 until we identified a difference that could be detected with 90% power. That difference was 0.16 D.

9.3 POPULATIONS FOR ANALYSES

The analyses datasets for each of the aims will include all participants enrolled in the study.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics will be presented as means and standard deviations for continuous, normally distributed variables, with medians and ranges for those skewed variables. Categorical data will be presented as percentages. Results of the analyses of both the primary and secondary aims will be

presented with 95% confidence intervals, as well as two-tailed p-values. Assumptions for each analysis will be checked as appropriate. Covariates to be considered include gender, ethnicity, parental myopia, visual activities (near work, time spent outdoors), pupil size, and accommodative lag. Compliance will be collected at each outcome visit using a compliance survey to solicit information from both parent and child. Based on the data collected, a definition of compliance will be determined from the percentage of time a given child spends awake and the amount of time the child spends wearing the lenses.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Specific Aim 1: test the hypothesis that thinner subfoveal choroidal thickness is associated with greater axial elongation

For the first aim we will fit repeated measures mixed regression models of axial length as a function of time relative to baseline. Choroidal thickness will be measured annually, providing four time points of data. The basic model will have the form:

$$\text{Axial elongation}_{ij} = A0 + A1*\text{Time}_{ij} + A2*Q + A3*Q*\text{Time}_{ij} + \beta_i + \varepsilon_{ij}$$

In the model **i** is the subject index and **j** the within-subject index for the subject's repeated measures. The term $\boldsymbol{\beta_i}$ is a random effect for subject. $\boldsymbol{\varepsilon_{ij}}$ is the within-subject residual error. The predictor **Q** is subfoveal choroidal thickness. As the model form indicates, subfoveal choroidal thickness will be added as both a main effect and an interaction with Time. The focus of interest is whether the subfoveal choroidal thickness moderates the effect of time. Thus the focus is to test the statistical significance of parameter A3.

We will control for previous BLINK Study treatment assignment, baseline SPHEQ, site, baseline age, gender, and ethnicity. For Aim 1 we will also control for the time of day at which the choroidal thickness measure was taken. In the basic model we will assume the mean axial length growth trajectory is linear in time. We will test the hypothesis by treating Time as a class variable and comparing the fit of the less constrained model to that of the basic model using a likelihood ratio test. Tests of hypotheses will use the best fitting model.

Specific Aim 2: test the hypothesis that less ipRGC activity (as measured by blue light-driven inputs to the pupil response) is associated with greater axial elongation

For the second aim, we will fit repeated measures mixed regression models of axial length as a function of time relative to baseline. Blue-light driven inputs, as measured by the pupillary response from the ipRGC, will be measured every 6 months, providing six time points of data because of the discontinuation of the 6 month visit due to COVID-19.

The basic model will have the form:

$$\text{Axial elongation}_{ij} = A0 + A1*\text{Time}_{ij} + A2*\text{pupillary response} + A3*\text{pupillary response}*\text{Time}_{ij} + \beta_i + \varepsilon_{ij}$$

In the model **i** is the subject index and **j** the within-subject index for the subject's repeated measures. The term $\boldsymbol{\beta_i}$ is a random effect for subject. $\boldsymbol{\varepsilon_{ij}}$ is the within-subject residual error. The predictor change is the pupillary response. As the model form indicates, a predictor will be added as both a main effect and an interaction with Time. The focus of interest in Aim 2 is whether the ipRGC activity moderates the effect of time. Thus the focus is to test the statistical significance of parameter A3.

We will control for previous BLINK Study treatment assignment, baseline SPHEQ, site, baseline age, gender, and ethnicity. We will also control for the season and the time of day at which the ipRGC measure was taken, as well as the environmental light exposure by the $\log_{10}$ lux-minutes of exposure from the Actiwatch data. In the basic model we will assume the mean axial length growth trajectory is linear in time. We will test the hypothesis by treating Time as a class variable and comparing the fit of the less constrained model to that of the basic model using a likelihood ratio test. Tests of hypotheses will use the best fitting model. Correlations between the pupillary responses, light exposure, and spherical equivalent will also be analyzed.

Specific Aim 3: test the hypothesis that exposure to lower light levels is associated with greater axial elongation

We will fit repeated measures mixed regression models of axial length as a function of time relative to baseline. Light level exposure will be measured every 6 months, providing six time points of data because of the discontinuation of the 6 month visit due to COVID-19. The basic model will have the form:

$$\text{Axial elongation}_{ij} = A0 + A1*\text{Time}_{ij} + A2*\text{average light exposure} + A3*\text{average light exposure}*\text{Time}_{ij} + \beta_i + \varepsilon_{ij}$$

In the model **i** is the subject index and **j** the within-subject index for the subject's repeated measures. The term $\boldsymbol{\beta_i}$ is a random effect for subject. $\boldsymbol{\varepsilon_{ij}}$ is the within-subject residual error. The predictor **Q** is the light exposure level as measured by the weekly average daily light exposure. As the model form indicates, the average daily light exposure will be added as both a main effect and an interaction with Time. The focus is whether the light exposure moderates the effect of time, i.e., the statistical significance of parameter A3.

We will control for previous BLINK Study treatment assignment, baseline SPHEQ, site, baseline age, gender, and ethnicity. In the basic model we will assume the mean axial length growth trajectory is linear in time. We will test the hypothesis by treating Time as a class variable and comparing the fit of the less constrained model to that of the basic model using a likelihood ratio test. Tests of hypotheses will use the best fitting model. Additional analyses will use the physical activity information from the Actiwatch 2. The average daily physical activity will be assessed using a model similar to that above to determine possible associations with axial elongation. An analysis using the mean amount of time per day spent in light levels >1000 lux (outdoor light levels) will also be done using similar methodology.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Specific Aim 1: test the hypothesis that long-term soft multifocal contact lens wear does not alter accommodative amplitude, lag of accommodation, or accommodative facility

Each accommodative measure will be associated with a tolerance interval, $[\Theta_{lower}, \Theta_{upper}]$. The tolerance intervals we will use are specified in the power analysis section. For each measure, we will test the equivalence of (1) the means of the +1.50D add group and the spherical CL group and (2) the means of the +2.50D add group and the spherical CL group. This will be done by showing the confidence intervals for the true group differences, estimated using the observed mean differences, are contained within $[\Theta_{lower}, \Theta_{upper}]$. We will thus be performing 6 tests, two contrasts for each of our 3 measures. The nominal alpha level will be adjusted using a Bonferroni correction to account for multiple testing and

ensure a family wise error rate of 0.05. Because there have been participants who did not crossover to the +2.50 D add lens, in addition to the planned analysis of intent-to-treat, we will complete a sensitivity analysis where these participants will be excluded. This will allow us to determine if these participants are affecting the results.

Secondary Specific Aim 2: test the hypothesis that soft multifocal contact lenses slow rather than merely delay myopia progression

We will fit a repeated measures mixed regression model of spherical equivalent as a function of time relative to baseline. For Secondary Aim 2 the time interval of interest is the growth trajectory of spherical equivalent over the first two years of the study, when all participants are wearing multifocal lenses. Spherical equivalent will be measured annually. Thus in the first two years there will be three time points of data. The basic model will have the form:

$SPHEQ_{ij} = A0 + A1*Time_{ij} + A2*Treatment + A3*Treatment*Time_{ij} + \beta_i + \varepsilon_{ij}$

The definitions of the indices, **β**, and **ε** are the same as in Aims 1-3. The aim's question predictor, BLINK Study treatment assignment (Treatment), is added as a main effect and as an interaction with Time. The aim's focus is to test whether treatment level moderates the effect of time. Thus the aim's focus is to test the statistical significance of parameter A3.

The model will control for site, baseline age, gender, and ethnicity. The following model variants will be considered. First, previous treatment level (spherical CLs, +1.50D add, and +2.50D add) will be considered in two ways: as a class and as an ordinal variable. Viewing previous treatment level as an ordinal variable has the potential to provide more power if there is a dose response to treatment. Second, time will be treated as both a quantitative and class variable. Model variants will be compared using likelihood ratio tests. Hypothesis testing will use the best fitting model.

Because there have been participants who did not crossover to the +2.50 D add lens, in addition to the planned analysis of intent-to-treat, we will complete a sensitivity analysis where these participants will be excluded. This will allow us to determine if these participants are affecting the results.

Secondary Specific Aim 3: test the hypothesis that there is no increase in myopia when switching from multifocal to single vision contact lenses

We will fit a repeated measures mixed regression model of spherical equivalent as a function of time relative to baseline. We will assume growth in spherical equivalent is linear with time. For Secondary Aim 3 the time interval of interest is the study's three years. Thus for this aim we will have four time points of data. The basic model will have the form:

$SPHEQ_{ij} = A0 + A1*Time_{ij} + A2*IND + \beta_i + \varepsilon_{ij}$

The definitions of the indices, **β**, and **ε** are the same as in Aims 1-3. IND is an indicator variable which is 0 for time points prior to year 3, and 1 for the final time point. The focus of the Secondary Aim 3 analysis will be the statistical significance of parameter A2. If statistically significant it would indicate, relative to years 0 to 2, there was a change in the slope of the spherical equivalent trajectory in the study's final year. The model will control for site, baseline age, gender, and ethnicity.

Because there have been participants who did not crossover to the +2.50 D add lens, in addition to the planned analysis of intent-to-treat, we will complete a sensitivity analysis where these participants will be excluded. This will allow us to determine if these participants are affecting the results.

9.4.4 SAFETY ANALYSES

The occurrence of AEs will be monitored to determine if there are unexpected events or SAEs as the study progresses.

One aim of the study will be switching all participants back into single vision contact lenses at the two-year examination in order to study potential rebound following the cessation of the treatment. These data are currently unavailable, and a strongly suggested research aim according to the FDA.

Two approaches to addressing safety will be taken. The first will be the monitoring of the data from the MiSight contact lens trial (NCT01729208). Participants from this study of a proprietary multifocal lens have been withdrawn from their treatment to evaluate the potential for rebound when returning to the single vision lenses. As these data become available, we will be able to determine what might be expected from the withdrawal of treatment. Without information about the estimated effect, the following will be executed.

In order to determine whether the rebound following the switch to single vision contact lenses at the two-year exam exceeds what would be expected, we will do an assessment when 50% of the participants have completed their thirty month visit. The change in axial length will be calculated between the two-year and thirty-month visit after the switch to single vision contact lenses. If the difference in the average axial length change across the subjects exceeds 0.15 mm, then progression would be considered significant enough to warrant discontinuing the rebound aim for the study for the remaining participants. This criterion represents half (six months worth) of the axial length elongation experienced by the single vision contact lens group in the BLINK Study.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be presented as means and standard deviations for continuous, normally distributed variables, with medians and ranges for those skewed variables. Categorical data will be presented as percentages. Results of the analyses of both the primary and secondary aims will be presented with 95% confidence intervals, as well as two-tailed p-values. Assumptions for each analysis will be checked as appropriate.

For the secondary aims, participants will be compared using their original BLINK allocation for comparative purposes.

9.4.6 PLANNED INTERIM ANALYSES

No interim analyses planned.

9.4.7 SUB-GROUP ANALYSES

None are planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed.

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses cannot be used as confirmatory proof for registration trials. All planned exploratory analyses should be specified in the protocol.

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

The Examiner is usually the person responsible for explaining the study to potential participants and for insuring that the informed consent process is appropriately completed. Study coordinators may also perform this task. 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 participants 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.
Signatures on the informed consent may be obtained by paper or electronic means. In rare situations the consent might also be done via telephone.
The following consent materials are submitted with this protocol:

- Assent-Bifocal Lenses v2
- Assent-Single Vision V2
- Parental Permission-Bifocal Lenses V3
- Parental Permission-Single Vision v3

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the

purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

While unanticipated, study discontinuation will follow this procedure. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants, NEI, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at The Ohio State University College of Optometry Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by The Ohio State University College of Optometry Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at The Ohio State University College of Optometry Data Coordinating Center.

Certificate of Confidentiality
To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

We will use information collected during the BLINK Study for purposes related to the BLINK2 Study and your child's continued eye care. De-identified data may be shared, made public, published, or used in future studies without additional permission from you, but it will not contain any information that could identify your child.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
Jeffrey Walline, OD, PhD, Study Chair	*Not applicable*
The Ohio State University	
338 West 10th Avenue, Columbus, OH 43210	
614-247-6840	
Walline.1@osu.edu	

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 on a weekly basis. 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

- NIH Program Officer

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.; and
• to implement changes suggested by the Data Monitoring and Oversight Committee.

10.1.6 SAFETY OVERSIGHT

To maintain participant safety throughout a clinical trial, an independent group of experts was 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. For the purposes of the BLINK2 Study, the DSMC will be converted to the Data Monitoring and Oversight Committee (DMOC). Among the responsibilities of the DMOC are the following:

- Reviewing the study design and informed consent and data collection procedures, and recommending protocol changes as deemed appropriate;
- Monitoring the trial conduct, 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 DMOC members, including the DMOC 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 DMOC.

10.1.7 CLINICAL MONITORING

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.
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 participants 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 participants through examinations
- Observation of examiners during examinations
- 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 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.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

At the onset of the BLINK2 Study, all study personnel will under training and certification prior to any participant contact. Training will take place at a Full Investigator group meeting, with written testing, and practical performance needing to be completed in order to become certified. New personnel added during the study will be trained by the clinical site PI, will take the written examination graded by the Data Coordinating Center, and certified following submission of practical results.

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. Coordinators at each site with review participant files and get errors corrected in a timely manner.

If the Data Coordinating Center receives study forms with information that is missing or with data that are not reasonable, a query will be created and sent to the clinic site. If the form is completed by the Examiner, every attempt should be made to determine the problem, and the problem should be corrected or an explanation should be provided. If the form is completed by a participant 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 participant or parent. The query should be completed and returned to the Data Coordinating Center within one month.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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 Center for Clinical and Translational Science (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 participants and parents to complete the surveys during the time of the visit. A link is provided to the participant/parent that takes them to the survey module to complete the required survey.

Several modules are collected from instruments (Grand Seiko, Lenstar, RapidX, and Actiwatch). 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. Interfaces will be written that will incorporate the data from the spreadsheets directly into REDCap forms.

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 change, the date it was made, and what it was replaced with is recorded. Original data are always retained.

10.1.9.2 STUDY RECORDS RETENTION

Research records will be maintained per the requirements of each research site, but at a minimum for at least two years.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to NIH Program Official and The Ohio State University College of Optometry Data Coordinating Center. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the publication of the primary aims by contacting Dr. Jones-Jordan.

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.

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.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

The study leadership in conjunction with the National Eye Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or IRB-related requirements.

N/A

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities

MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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