Study Implementation document: Protocol

CLINICAL EVALUATION OF BIOFINITY MULTIFOCAL TORIC CONTACT LENSES

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[redacted]

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DOCUMENT CHANGE HISTORY

Version	Originator	Description of Change(s)	Date
1.0	Myhanh Nguyen	Original Protocol	21 February 2018

1 Introduction

CooperVision, (CVI) is extending the power range of the commercially available Biofinity silicone hydrogel contact lenses to include multifocal toric silicone hydrogel contact lenses (Biofinity MFT).

This study is to evaluate the clinical performance of the Biofinity MFT lenses.

2 Study Objective

The objective of this non-dispensing clinical study is to compare the clinical performance of Biofinity Multifocal Toric (BF MFT) with Proclear Multifocal Toric (PC MFT) contact lenses.

The primary variable of interest is:

- Visual acuity (VA)

The secondary variable of interest is:

- Subjective assessments of visual performance

[redacted]

2.1 Study Hypothesis

The study hypothesis is that the Biofinity Multifocal Toric lenses will not be clinically inferior to Proclear Multifocal Toric lenses.

3 Study Design

This non-dispensing, subject masked, randomized, bilateral crossover study will compare the clinical performance of Biofinity Multifocal Toric contact lenses.

Up to 20 subjects, who have worn soft contact lenses in the last six months, will be enrolled.

This study will be composed of two parts. Part A will involve a screening/baseline visit for the determination of subject's contact lens prescription based on their spectacle refraction. With the

information obtained from Part A, Biofinity Multifocal Toric and Proclear Multifocal Toric contact lenses will be made to order on a per-patient basis for use in Part B to assess the clinical performance of the lenses.

Subjects must be able to participate in both parts of the study; Part A of the study will last approximately 1-2 hours duration and Part B will last approximately 3-4 hours duration.

4 Ethics Review / Statement of Compliance

4.1 Relevant Standards / Guidelines

This implementation document has been developed in accordance with the following:

- ISO 14155 Clinical Investigation of Medical Devices for Human Subjects
- 21 CFR 812.2(b) Investigational Device Exemption – Abbreviated Requirements
- ISO 11980 Contact Lens and Lens Care products – Guidance for Clinical Investigations
- ICH Harmonized Tripartite Guideline for Good Clinical Practice
- Declaration of Helsinki

4.2 Institutional Review Board

This study will be conducted in accordance with Institutional Review Board regulations (U.S. 21CFR Part 56.103) or applicable IEC regulations. Copies of all IRB/IEC correspondence with the investigator/sponsor will be kept on file.

The conduct of this study will be approved by The University of Manchester committee on the ethics of research on human beings (hereafter referred to as Manchester UREC) prior to commencement.

4.3 Informed Consent

Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is carried out.

5 Clinical Trial Registration

This study will be registered with ClinicalTrials.gov in accordance with Section 801of the Food and Drug Administration Act (FDAA) which mandates the registration of certain clinical trials of drugs and medical devices.

6 Potential Risks and Benefits to Human Subjects

There might not be direct benefits to the subjects in this study. However, participation in a study may contribute to scientific research information that may be used in the development of new contact lens products. In addition, subjects will receive an examination of the front part of their eyes and may have the opportunity to try a different type of soft contact lenses and/or different lens care products at no cost to them.

The investigational contact lenses used in this study are CE marked and intended for daily wear (NOT extended wear) with usage of up to four hours only, in contrast to the average wearing time of 10-16 hours for daily wear lenses. In addition, this study is a non-dispensing study, meaning the lenses are not dispensed to subjects to take home and lens wear will be monitored closely by the investigators.
This study is considered to be a non-significant risk study based on United State Food and Drug administration (FDA) and International Standards Organization (ISO) guidelines due to no potential of serious risk to the health, safety, or welfare of a subject.

Complications that may occur during the wearing of contact lenses include discomfort, dryness, aching or itching eyes, excessive tearing, discharge, hyperemia and variable or blurred vision. More serious risks may include photophobia, iritis, corneal edema and eye infection. Although contact lens-related infections are very infrequent, the possibility does exist. The incidence of infection due to day-wear soft lenses is 0.035%. An infection will usually occur only in one eye. This risk is assumed by 35 million Americans who currently wear contact lenses.

Routine clinical procedures including auto-refraction, auto-keratometry, visual acuity, anterior ocular health assessment, and contact lens fitting may be used. In addition, high magnification imaging of the lens fit may be made using 35 mm or digital cameras.

7 Materials and Methods

7.1 Subjects

Up to twenty subjects will be needed to complete the study. Each subject will be given a unique ID number. Additionally, all subjects must meet the study inclusion and exclusion criteria listed below. Potential subjects will be identified from the investigators' clinic database records and/or will be actively recruited by advertisements circulated at the investigational sites approved by the appropriate IRB.

Inclusion Criteria

A person is eligible for inclusion in the study if he/she:

- Has had a self-reported oculo-visual examination in the last two years.
- Is aged 40–75 years, inclusive and has full legal capacity to volunteer.
- Has read and understood the participant information sheet.
- Is willing and able to follow instructions and maintain the appointment schedule.
- Is able to participate in Parts A and B related to this work.
- Has a contact lens spherical prescription between +10.00 to -10.00D (inclusive).
- Has an Add component to their spectacle refraction (between +0.75 and +2.50DS).
- Has astigmatism between -0.75 and -5.75DC (based on the vertexed ocular refraction in each eye.
- Can be satisfactorily fitted with the study lenses.
- Is correctable to a visual acuity of 20/40 (0.30 logMAR) or better (in each eye) with their habitual vision correction or 20/25 (0.10 logMAR) best-corrected.
- They have successfully worn soft contact lenses in the last six months
- Has clear corneas and no active ocular disease.
- Has not worn lenses for at least 12 hours before the examination.
- Has an up-to-date pair of spectacles.

Exclusion Criteria

A person will be excluded from the study if he/she:

- Has never worn contact lenses before.
- Has any systemic disease affecting ocular health.

- Is using any systemic or topical medications that will affect ocular health.
- Has any ocular pathology or severe insufficiency of lacrimal secretion (moderate to severe dry eyes) that would, in the opinion of the investigator, affect the wearing of contact lenses.
- Has persistent, clinically significant corneal or conjunctival staining using sodium fluorescein dye that would, in the opinion of the investigator, be problematic for their participation in the study.
- Has any clinically significant lid or conjunctival abnormalities, active neovascularization or any central corneal scars.
- Is aphakic.
- Has undergone corneal refractive surgery.
- Has a history of anaphylaxis or severe allergic reaction.
- Has diabetes or an infectious or immunosuppressive disease which could contraindicate contact lens wear or pose a risk to the investigator.
- They are pregnant or breast-feeding.
- Is participating in any other type of eye-related clinical or research study.

7.1.1 Subject Identification

Each subject will be given a unique ID number. Subject ID numbers will be assigned to the subjects sequentially and in ascending order, and will not be reused in the event of screen failure, subject dropout or discontinuation from the study.

7.2 Study Materials

7.2.1 Contact Lens

Subjects will be randomized to receive either the Test or Control lens as the first pair of contact lenses as per the randomization schedule. The lenses used in this study will be provided by the Sponsor.

Details of the CE marked contact lenses are shown in Table 1.

Table 1: Study lenses

	Lens 1	Lens 2
Name	Biofinity Multifocal Toric	Proclear Multifocal Toric
Manufacturer	CooperVision	CooperVision
Material	Comfilcon A	Omafilcon B
EWC (%)	48%	62%
Base Curve (mm)	8.7	8.4 / 8.8
Diameter (mm)	14.5	14.4
Spherical powers (DS)	+10.00 to -10.00 (0.50 steps after ±6.50D)	+20.00 to -20.00 (0.50 steps after ±6.50D)
Cyl Powers (DC)	-0.75 to -5.75 (0.50 steps)	-0.75 to -5.75 (0.50 steps)
Axis (°)	5 to 180 (5 degree steps)	5 to 180 (5 degree steps)
Add (D)	+1.00, +1.50, +2.00, +2.50 (D & N)	+1.00 to +4.00 (D & N)

7.2.2 Contact Lens Care

No contact lens care is required for this study as lenses are to be worn in the clinic only.

7.2.3 Storage of Lenses

The study materials must be stored in a secured area. All lenses should be stored at controlled room temperature (59-86°F, 15-30°C).

7.2.4 Clinical Supply Inventory

All lenses will be supplied by the Study Sponsor. The investigator must keep an accurate account of the study product during the study. A detailed inventory must be completed for study supplies. The study supplies are to be used in accordance with the implementation document by subjects who are under the direct supervision of an investigator.

7.2.5 Disposal of Consumables

This study dispenses consumables (lenses) to participants for use during the study. All unused and used materials will be returned to the Sponsor at the end of the study unless the investigator is otherwise directed by the study Sponsor. All worn lenses will be collected at the completion of the study in screw top contact lens cases filled with either a suitable multi-purpose solution or saline.

7.2.6 Masking and Control of Study Materials

The contact lens coding will be masked to the subject. Masking to the subject will be achieved by minimising the exposure to the device label.

7.2.7 Ordering and Accountability of Study Materials

The test and control lenses will be provided by the sponsor. The investigator must complete an accurate account of the study product at the completion of the study. A detailed inventory must be completed for study supplies.

7.3 Visit Schedule and Procedures

There will be a minimum of two scheduled visits as follows:

7.3.1 Screening/Baseline Visit (Part A)

The subjects should attend wearing their spectacles, not having worn their own contact lenses for a minimum of 12 hours prior to this visit.

Procedures to be Performed

The following evaluations will be performed to assess eligibility according to the Inclusion and Exclusion Criteria at the baseline visit only:
The following evaluations will be performed on all subjects:

1. The subject will be required to read and sign an Informed Consent Form prior to enrolment. When the subject has signed the consent form, the subject will then be considered to be enrolled in the study
2. Subject demographics (age, sex, medications, allergies)
3. Contact lens wearing history including:
    - Habitual lenses, modality, average wear time and comfortable wear time
4. Auto-refraction and Auto-keratometry measures will be recorded
5. Pupil size measurements (OD, OS) (high and low illuminationat distance (equivalent to 6M) and near (40cm)
6. HVID measurement
7. Baseline distance high contrast logMAR visual acuity (OD, OS) with spectacles or habitual Rx in phoropter or trial frame
8. Monocular sphero-cylindrical refraction (D) followed by binocular balance (endpoint is the most plus or least minus that gives the best binocular distance visual acuity)
9. Near addition as determined by NRA/PRA/BCC (D)

10. Dominant eye test (sensory): the dominant eye will be determined using the +2.00D blur test
11. Visual acuities with best correction:
    - Best-corrected high contrast, high illumination*, distance (equivalent to 6M), logMAR acuity (OD, OS and OU) (natural pupil)
    - Best-corrected high contrast, high illumination*, near (40cm), logMAR acuity (OD, OS and OU) (natural pupil)

      **High room illumination: Overhead lights on = 300-600 lux*
12. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI Grading scales (Appendix 1)
13. Saline Rinse
14. Confirm subject meets the inclusion/exclusion criteria
15. The information required from the spectacle refraction includes:
    - Spectacle refraction (vertex corrected assuming a 15 mm vertex distance) (D)
    - Keratometry readings (D)
    - Dominant eye (sensory)
    - Add power (D)
16. The information from #15 above will be used to determine the contact lens prescription based on the fitting guides (Appendix 2).
17. The site will send the contact lens prescriptions to the Sponsor who will then order the contact lenses.
18. The subject will then be discharged and asked to return when lenses are available for Part B of the study. Subjects will be free to return to wearing their habitual lenses until the follow-on study begins. Study personnel will contact them to schedule Part B of the study upon lens arrival.

7.3.2 Lens Performance Assessment Visit (Part B)

The subjects should attend this visit wearing their spectacles, not having worn their own contact lenses for a minimum of 12 hours prior to this visit.

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1. Details of ocular history and contact lens wearing history will be checked for any changes since the last visit.
2. Baseline distance high contrast logMAR visual acuity (OD, OS) with spectacles or habitual Rx in phoropter or trial frame
3. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI Grading scales (Appendix 1).
4. Saline Rinse

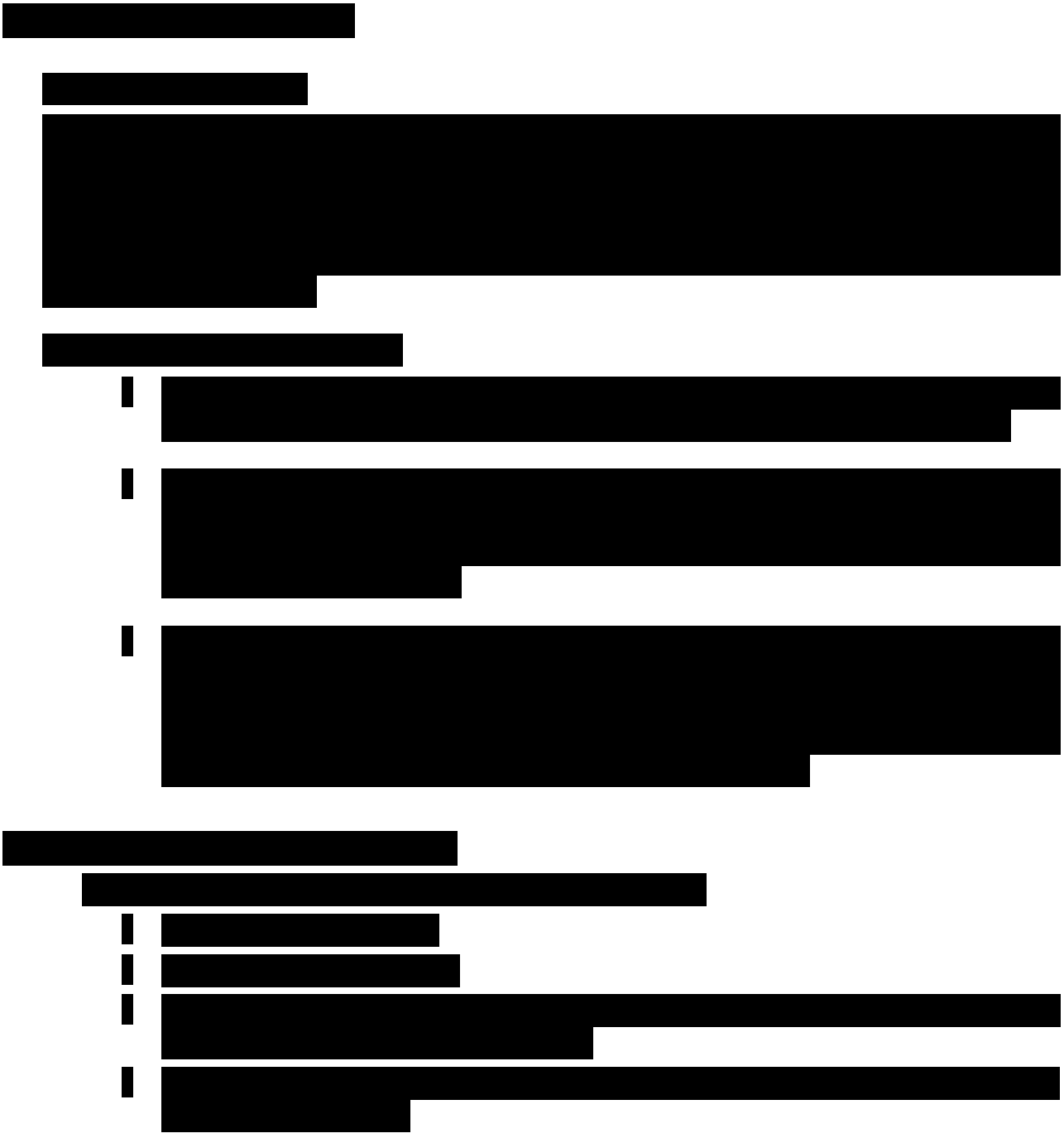
7.3.3 Lens Pair 1

7.3.3.1 Lens Insertion

1. The first lens pair, manufactured from information obtained in Part A, will be fitted according to the randomization table.
2. Lenses will be allowed to settle for at least 15 minutes.

7.3.3.2 Visual Acuity / Lens Fitting

1. Binocular and monocular visual acuity will be assessed at distance (equivalent to 6M) and near (40cm) before over-refraction:
    - HIHC* logMAR VA (equivalent to 6M, 40cm) – (OD, OS, OU)
2. [redacted]



7.3.3.5 Contact lenses to be removed by investigator and retained for return to the Sponsor.

7.3.4 Lens Pair 2 and Exit

1. The second lens type will be inserted according to randomization schedule.
2. The same procedures outlined in Section 7.3.3 will be repeated.
3. Subjects to assess their preference between Lens Pair 1 and 2 for a number of considerations according to the CVI guidelines in Appendix 3 (5 point Likert scale) (Strong Pair 1, Slight Pair 1, no preference, Strong Pair 2, Slight Pair 2):
   - [redacted]
   - Overall Vision Preference
   - [redacted]
4. Contact lenses to be removed by investigator and retained for return to the Sponsor.
5. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI Grading scales (Appendix 1).
6. Exit high contrast logMAR visual acuity (OD, OS) with spectacles or habitual Rx in phoropter or trial frame
7. The subject will be discharged and asked to sign the exit statement.

7.3.5 Summary of Visits and Procedures

Table 2 summarizes the visits and procedures for the study.

Table 2: Summary of Visits and Procedures

	Screening/ Baseline visit	Lens fitting and exit visit
Informed Consent	✓	
Meet inclusion/exclusion criteria	✓	✓
Demographics	✓	
History at baseline	✓	✓
VA with spectacles or refraction	✓	✓
Auto-refraction & keratometry	✓	
Pupil size / HVID	✓	
Sphero-cylindrical refraction	✓	

Best corrected (sphero-cyl) logMAR VA monocular and binocular	✓	
Add determination	✓	
Dominant eye test (+2.00 blur test)	✓	
Instillation of lens at office	–	✓
[redacted]	[redacted]	[redacted]
logMAR VA with contact lenses	–	✓
[redacted]		[redacted]
Slit lamp findings	✓	✓
[redacted]	[redacted]	[redacted]
Exit study		✓

8 Adverse Event Reporting

8.1 Adverse Event Definitions

An ‘adverse event’ refers to any undesirable clinical occurrence in a participant, whether it is considered to be device-related or not. Adverse events (AE) may be classified as ‘unanticipated adverse device effects,’ ‘serious adverse events,’ ‘significant adverse events,’ or ‘non-significant adverse events,’ as defined below. All ocular AEs will be recorded and reported to the sponsor, as will any serious non-ocular adverse events .

AE classification, coding (for reporting to the sponsor) and examples are provided in the following table of Contact Lens Adverse Event Classification and Reporting table:

Classification	Definition
Serious Adverse Event	Those events that are life-threatening, or result in permanent impairment of a body function, or permanent damage to a body structure or necessitate medical (therapeutic) or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
Significant Adverse Event	Those non-serious adverse events that occur with contact lens usage that are not sight-threatening but are usually symptomatic and may warrant therapeutic management and /or temporary or permanent discontinuation of contact lens wear.
Non-Significant Adverse Events	Those less severe non-serious adverse events that occur with contact lens usage that are not sight-threatening, may or may not be symptomatic and may warrant palliative management, such as ocular lubricants or temporary interruption of contact lens wear.
Unanticipated Adverse Device Effect	Adverse events in a clinical trial that were not previously identified in the protocol in terms of nature, severity, or degree of incidence. An Unanticipated Serious Adverse Device Effect is an unanticipated adverse event that is serious in nature and caused by or associated with the device and is considered reportable.

Code	Condition	Reporting
Serious Adverse Events		
01	Presumed infectious keratitis or infectious corneal ulcer	Notify sponsor as soon as possible, **within 24 hours;** IRB reporting as per requirements
02	Permanent loss of ≥ 2 lines of best spectacle corrected visual acuity (BSCVA)	
03	Corneal injury that results in permanent opacification within central cornea (6mm)	
04	Uveitis or Iritis (e.g. presence of anterior segment inflammation as described in ISO 11980, Annex B)	
05	Endophthalmitis	
06	Hyphema	
07	Hypopyon	
08	Neovascularization within the central 6mm of cornea	
00	Other serious event	
Significant Adverse Events		
11	Peripheral (outside central 6mm), non-progressive, non-infectious ulcer	Notify sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
12	Symptomatic corneal infiltrative event	
13	Superior epithelial arcuate lesions (SEALs) involving epithelial split	
14	Corneal staining ≥ dense coalescent staining up to 2mm in diameter (e.g. moderate, ISO 11980 grade 3)	
15	Corneal neovascularization ≥ 1.0mm vessel penetration (e.g. ≥ ISO 111980 Grade 2), if 2 grade change from baseline	
16	Any temporary loss of ≥ 2 lines BSCVA for ≥ 2wks	
17	Any sign and/or symptom for which subject is administered therapeutic treatment or which necessitates discontinuation of lens wear for ≥ 2 weeks	
10	Other significant event	

Non-significant Adverse Events		
21	Conjunctivitis (bacterial, viral or allergic)	Notify sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
22	Papillary conjunctivitis if ≥ mild scattered papillae/follicles approximately 1mm in diameter (e.g. ISO 11890 Grade 2), if 2 grade change from baseline	
23	Asymptomatic corneal infiltrative events	
24	Any sign and/or symptom for which temporary lens discontinuation for > 1 day is recommended (if not already classified)	
20	Other sign and/or symptom warranting classification as a non-significant adverse event	

Normal or adaptive symptoms

Transient symptoms such as end-of-day dryness, lens awareness, itching or burning or other discomfort may occur with contact lens wear and may occasionally reduce wearing time. ***These are not reported as adverse events unless in the investigator's opinion they are unexpected in nature, severe or have a high rate of occurrence.***

This clinical study will also ascertain satisfaction or preference with subjective attributes, such as comfort, vision or lens handling. Responses to these subjective questionnaires will not be considered as Adverse Events.

8.2 Procedures for Adverse Events

Treatment of an adverse event will depend on its nature and severity. Based on the clinical judgment of the investigator the subject may be referred to an ophthalmologist for treatment. The investigator will attempt to determine whether the reaction is related to the test device or a result of other factors. An Adverse Event Form will be completed for each adverse event. If both eyes are involved, a separate Adverse Event Form will be completed *for each eye*. Whenever possible, the adverse event will be photo-documented.

Expenses incurred for medical treatment as part of study participation will be paid by the sponsor (bills and prescription receipts kept). The subject must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.

8.3 Reporting Adverse Events

All potential Serious and Unanticipated Adverse Device Effects that are related or possibly related to subject participation will be reported to the Principal Investigator and the sponsor within 24 hours

of the investigator becoming aware of the event. The Principal Investigator will report the event to the IRB as soon as possible (by fax, mail/delivery, phone, or email). All fatal or life threatening events will be reported immediately to the IRB.

Significant and Non-Significant Adverse Events will be reported to the sponsor as soon as possible, but no later than 5 working days after the occurrence.

Sponsor contact details are:

Contact:	Clinical Operations, CooperVision
Email:	[redacted]
Phone:	[redacted] or [redacted] / Fax: [redacted]
Address:	5870 Stoneridge Dr. Suite 1 Pleasanton, CA 94588

8.4 Discontinuation from the Study

A subject's study participation may be discontinued at any time if, in the opinion of the sponsor or the investigator, it is in the best interest of the subject. All discontinuations will be fully documented on the appropriate study forms and the Discontinuation Form will be completed.

9 Device Malfunctions

A device malfunction means the failure of the device to meet its performance specification or otherwise perform as intended. *Any defective lens that is likely to cause or contribute to a Serious Adverse Event should be reported to the Principal Investigator and the sponsor* ***within 24 hours*** *of the investigator becoming aware of the malfunction.*

Other defective lenses should be reported to the Sponsor as soon as possible.

This clinical study will also ascertain satisfaction or preference with subjective attributes such as comfort, vision, or lens handling. Responses to these subjective questionnaires will not be considered as complaints or Device Malfunctions.

10 Statistical Analysis

10.1 Statistical Plan

Summary statistics will be produced (e.g. mean, standard deviation). Paired t test will be used to compare slit lamp biomicroscopy, lens fit and subjective scores between study lens types. Repeated Measures Analysis of Variance (ANOVA) or paired analysis will be used to compare the variables between study visits. The critical alpha level for statistical significance will be set at $p \leq 0.05$, with adjustment for multiple comparisons.

All participants who were evaluated will be used in the analysis. In the event of missing data, individual data points will be excluded in the analysis and not extrapolated from the collected data.

11 Data Quality Assurance

11.1 Study monitoring

Site qualification of the investigative site has been completed to ensure that the site facility is adequate, personnel are qualified and resources are satisfactory to conduct clinical studies for the sponsor. The protocol will be reviewed by the investigators prior to enrollment of the first subject. This will involve an overview of the protocol, which includes information on study objectives, inclusion and exclusion criteria, study visits and adverse event reporting. Data collection forms will also be reviewed and this will provide an opportunity to discuss any questions.

During the course of the study, verification will be conducted to confirm that written informed consent was obtained prior to each subject's participation in the study using the IRB approved ICF.

[redacted]

- [redacted]

[redacted]

[redacted]

Prior to final data freeze, a close-out visit/discussion may be warranted to check for accuracy and completeness of records. The sponsor or sponsor's representatives will be authorized to gain access to the source documentation for the purposes of monitoring and auditing the study.

11.2 Record keeping

Detailed records of all study visits will be made using the Case Report Forms (CRFs). All data recorded on forms will be in ink. Any corrections to the forms will be initialed and dated at the time they are modified.

11.3 Record retention

Following study completion, data will be available in electronic and/or paper format for audit, sponsor use, or subsequent analysis. The original clinical raw data (including completed CRFs and Informed Consent forms) will be retained according to guidelines set forth in the general work agreement with the site. The Sponsor will be notified and consulted if ever the files are to be destroyed. In the event that this implementation document is indicated for design verification and validation purposes, as indicated on the title page, all original raw data forms and completed CRFs will be forwarded to the sponsor at completion of the final report.

11.4 Data Entry / Data Management

Data will be entered into an electronic spreadsheet. Study staff will only be able to modify the data file via password entry. The investigators will be responsible for the data integrity, and complete data entry for each visit. The investigator will send the data collected to the study sponsor within approximately 5 business days after the last subject completes the final visit.

11.5 Confidentiality

This study is confidential in nature. All information gathered during this study is proprietary and should be made available only to those directly involved in the study. Information and reports arising from this project are the property of the sponsor.

All records will also be handled in accordance with HIPAA (1996) standards.

11.6 Publication

Due to the confidential and proprietary nature of the clinical study, any presentation and/or publication including but not limited to those made at scientific meetings, in-house, in peer-review journals, professional publications, etc. need to be approved by the sponsor.

12 Study Costs

The sponsor will compensate the clinical site and the subjects for their time and participation in this voluntary study.

Expenses incurred for medical treatment as part of study participation will be paid by the sponsor (bills and prescription receipts kept). The participant must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.