# Clinical investigation plan

## C19-654 (EX-MKTG-105)

A clinical evaluation of the Biofinity Energys soft contact lens in users of digital devices

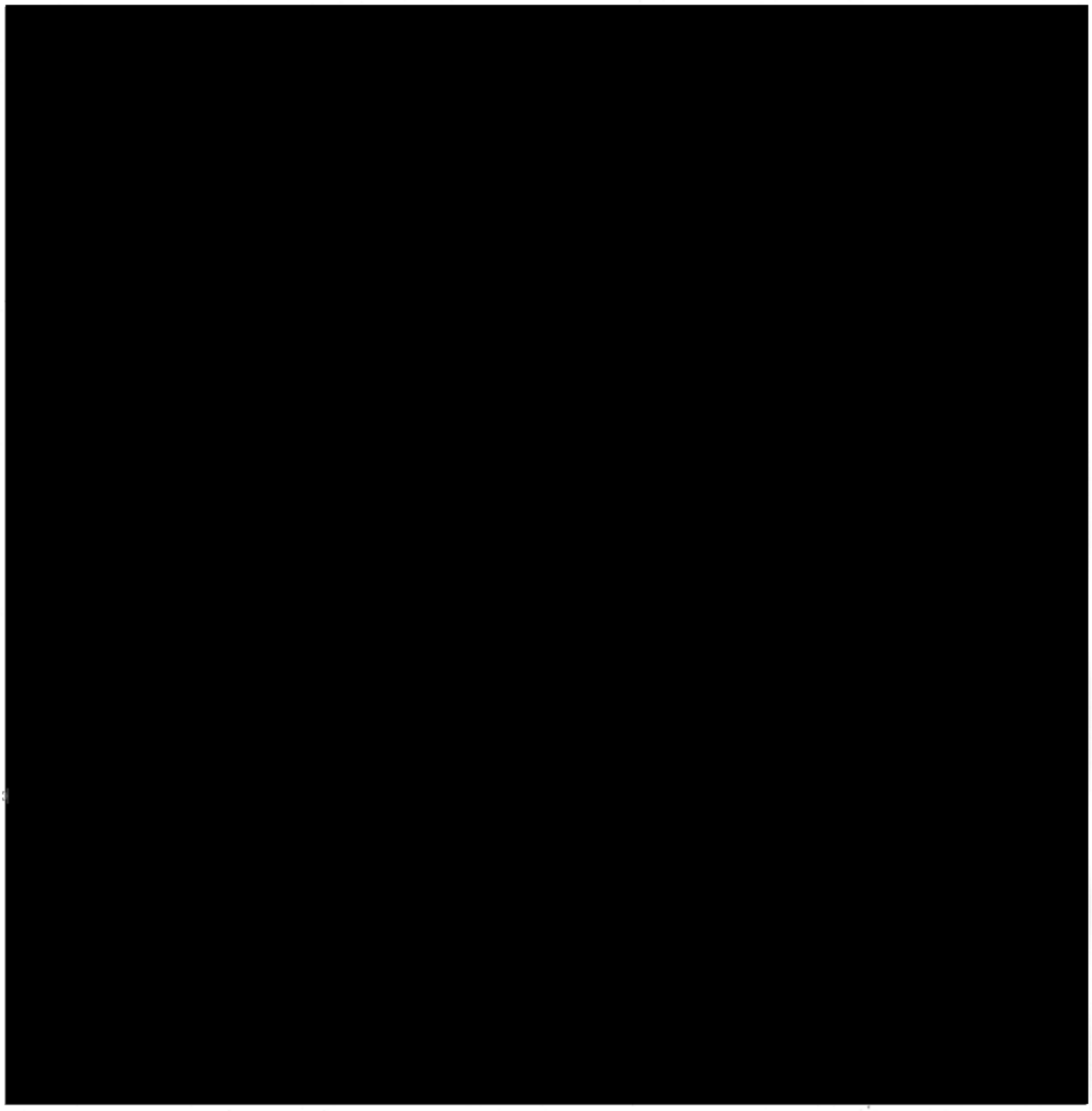
**A clinical evaluation for CooperVision Inc.**

**Principal Investigator**
Carole Maldonado-Codina

**May 2019**

# Contents





| Visit | Procedures |
|---|---|
| Information and consent presentation | Short on-line presentation of study aims and procedures |
| Initial visit | Informed consent taken<br>Ocular history<br>[redacted]<br>Cover test<br>[redacted] CVS-Q questionnaire<br>[redacted]<br>Confirmation of eligibility<br>Randomisation to treatment type<br>[redacted]<br>Contact lens application/removal/education session (CL group only) |
| 2 week visit (CL group only) | Ocular history<br>[redacted] CVS-Q questionnaire<br>[redacted] |
| 1 month visit | Ocular history<br>[redacted] CVS-Q questionnaire<br>[redacted] |
| 2 month visit | Ocular history<br>[redacted] CVS-Q questionnaire<br>[redacted]<br>Exit form signed and payment issued |

**Table 1: Study summary.**

# Section 1. Overview

## 1.1 Background

This project seeks to compare the clinical performance and subjective acceptance of the Biofinity Energys contact lens (CooperVision Inc.) when compared to single-vision spectacles in subjects who have never worn contact lenses and who use digital devices (phones, tablets, laptops, desktop computers) for at least 4 hours per day on at least 5 days per week.

## 1.2 Personnel

This work will be conducted at Eurolens Research, The University of Manchester under the general direction of Philip Morgan PhD MCOptom FAAO FBCLA. The Principal Investigator for the work is Carole Maldonado-Codina PhD MCOptom FAAO FBCLA.

## 1.3 Study objectives

The aim of this clinical work is to compare the clinical performance and subjective acceptance of Biofinity Energys (CooperVision Inc.) contact lens when compared to single-vision spectacles in subjects who use digital devices (phones, tablets, laptops, desktop computers) for at least 4 hours per day on at least 5 days per week. Seventy-six subjects will be randomised to use either their habitual spectacles or the study contact lenses for two months. Subjects will be asked to complete the Computer Vision Syndrome Questionnaire (CVS-Q) at each visit which is a validated 16-item questionnaire designed to measure visual symptoms related to the use of digital devices. The CVS-Q investigates both 'internal' (burning, itching, tearing, redness, dryness) and 'external' symptoms (e.g. eye pain, double vision, headache, blurred vision).

## 1.4 Study design

This will be a randomised, open label, parallel group study, in which 76 subjects will be randomised to either continue wearing their habitual spectacles, or the Biofinity Energys contact lens, for a period of two months.

## 1.5 Statistical considerations

As such, these will be compared using linear regression models or other parametric methods. Deviations

from this statistical plan will be discussed in the final report. Deviations may be necessary due to differences between the actual data distribution compared with the anticipated data distribution.

### 1.5.1 Power analysis

Using data from the literature and assuming a superiority study design, 34 subjects are required to use each treatment (contact lenses or spectacles) for 90% power, assuming a standard deviation of CVS-Q score of 4.0 units and a meaningful difference of score of 3.2 units (5% of the amplitude of the CVS-Q). To allow for discontinuations, 38 subjects will be randomised into each group, meaning 76 subjects in total.

## 1.6 Risk analysis

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 the daily wear nature of the study. With the potential benefit of this study, the work is considered to be ethically justifiable. Ethical approval will be sought from the University of Manchester Senate Committee on the Ethics of Research on Human Beings (hereafter referred to as Manchester UREC). The work where practical will be conducted in accordance with the ICH Good Clinical Practice Guidelines and the international standard BS EN ISO 14155:2011 ‘Clinical investigation of medical devices for human subjects’.

# Section 2. Resources

## 2.1 Subject selection

In this work 76 subjects will be recruited.

### 2.1.1 Subject withdrawal and replacement

This study includes up to four clinical visits. Once the study consent form is signed, the subject is considered to be enrolled on the study. Subjects who have signed the consent form, but who have not completed the dispensing visit will usually be replaced. All subject data will be included in the final analyses unless there are strong grounds for exclusion; such grounds will be detailed in the final report. At the end the study, all subjects will sign a study exit form.

### 2.1.2 Subject recruitment

Subjects will be recruited by one or more of following means:

1. Posting study details on The University of Manchester's 'Research Volunteers' website.
2. Correspondence to existing wearers on the Eurolens Research database of subjects.
3. Advertising through a variety of media via a format separately approved by Manchester UREC.

### 2.1.3 Inclusion criteria

Subjects will only be eligible for the study if:

1. They are between 18 and 35 years of age (inclusive).
2. They understand their rights as a research subject and are willing and able to sign a Statement of Informed Consent.
3. They are willing and able to follow the protocol.
4. They are a 'neophyte' (i.e. someone who has not worn contact lenses previously, with the exception for the purposes of a trial fitting, lasting up to one week).
5. They have a contact lens spherical prescription between -1.00 to -6.25D (inclusive) based on the ocular refraction.
6. They have a cylindrical correction of -0.875DC or less in each eye based on the ocular refraction
7. They own and habitually wear single vision spectacles used for both distance and near vision, including computer and digital device use.

8. Their single vision spectacles have a mean sphere equivalent within ±0.50D of that of the refraction found in the study for each eye (after having taken lens effectivity into account).
9. They are willing to be fitted with contact lenses and understand they may be randomised to either group.
10. They are willing to wear the contact lenses (if relevant) or spectacles for at least 8 hours per day, 5 days per week.
11. They typically use digital devices for a minimum of 4 hours per day, 5 days per week.
12. They agree not to change the spectacles they will wear for digital device use for the duration of the study.
13. They agree not to participate in other clinical research for the duration of the study.

### 2.1.4 Exclusion criteria

Subjects will not be eligible to take part in the study if:

1. They have an ocular disorder which would normally contra-indicate contact lens wear.
2. They have a systemic disorder which would normally contra-indicate contact lens wear.
3. They are using any topical medication such as eye drops (including comfort drops) or ointment on a regular basis.
4. The spectacles they use for digital device viewing on the study have been made with specialist features for computer use, digital eye fatigue or are multifocal/bifocal.
5. They are aphakic.
6. They have had corneal refractive surgery.
7. They have any corneal distortion resulting from previous hard or rigid lens wear or have keratoconus.
8. They are pregnant or breastfeeding.
9. They have any infectious disease which would, in the opinion of the investigator, contraindicate contact lens wear or pose a risk to study personnel; or they have any immunosuppressive disease (e.g. HIV), or a history of anaphylaxis or severe allergic reaction.
10. They have evidence of a heterotropia or decompensating heterotropia on cover test.
11. They have a history of having been prescribed prism in their spectacles (by self report).

12. They have taken part in any other contact lens or care solution clinical trial or research, within two weeks prior to starting this study.

## 2.2 Subject discontinuation

In general, subjects should be discontinued at any time, if it is in their best interests, as judged by the investigator. Reasons for this may include clinical signs of grade 3 or more, lack of motivation, discomfort, repeated refusal to follow instructions or the use of non-study products such as solutions or lenses. Subjects will be discontinued if a serious adverse event occurs or if they miss two or more planned consecutive visits. Subjects who fail to satisfy all the inclusion and exclusion criteria will be discontinued and replaced. Subjects may choose to leave the study at their own request. All discontinuations will be carefully recorded.

## 2.3 Safety parameters, adverse events and concurrent illnesses

The key safety parameters are the serious and significant adverse events listed in Appendix A (adverse events are classified as 'serious', 'significant' or 'non-significant'). Clinical assessment is made at the study visit(s) for these parameters. The presence of any ocular adverse event will be recorded on the eCRF and reported to the Sponsor using CVI report forms, and those ocular adverse events described as 'serious' or 'significant' will be detailed in the final report. Similarly, any concurrent illness that is likely to impact on the relevance and quality of the captured data will be noted on the case report form.

### 2.3.1 Investigator obligations

At all times the investigator will act in the best interest of the subject. Referral or treatment of an adverse event or other clinical finding should be initiated in the best clinical judgement of the investigator, irrespective of the participation in the clinical study.

### 2.3.2 Reporting obligations

In the case of a 'serious' or 'significant' adverse ocular event, the Principal Investigator will notify the Industrial Contact Person as soon as possible. Manchester UREC and any regulatory authorities will be informed as required.

## 2.4 Study termination

If it becomes necessary to terminate the study earlier than planned, the Industrial Contact Person will notify the Principal Investigator who will end the study with the cooperation of other staff members. Manchester UREC will be informed.

## 2.5 Protocol deviations and device deficiencies

Any deviations from this protocol will be recorded, and reported to the Industrial Contact Person as appropriate. Manchester UREC will be informed as necessary. Device deficiencies will be recorded and reported to the Industrial Contact Person.

### 2.5.1 Protocol amendments

Any amendments will be agreed between the Industrial Contact Person and the Principal Investigator with the cooperation of other staff members. Amendments will be recorded, identified and distributed. Approval from Manchester UREC will be obtained as necessary.

## 2.6 Study resources

Study products will be stored according to the manufacturer's product instructions.

### 2.6.1 Lenses

Details of the study lenses are provided in Table 2. The lens is CE marked. Initial lens selection will be as indicated by the manufacturer fitting guidelines.

| Name | Biofinity Energys |
|---|---|
| Manufacturer | CooperVision Inc. |
| Material | comfilcon A |
| EWC (%) | 48 |
| BOZR (mm) | 8.6 |
| Diameter (mm) | 14.0 |
| Spherical powers (D) | -0.50 to - 6.00 (0.25 steps) |

**Table 2: Study lenses.**

#### 2.6.1.1 Use of lenses

Study contact lenses will be worn on a daily wear, re-useable basis. [redacted] The lenses will be disinfected and stored using PureMoist (Alcon Vision Care) and the use of comfort drops will not be allowed. The lenses are also to be worn for a minimum of 2 hours before attending the follow-up visits (CL group only).

### 2.6.2 Inventory control

All study lenses will be supplied by CooperVision Inc. All worn lenses will be discarded. Unworn lenses will be returned [redacted]

[redacted]

### 2.6.3 Clinical equipment

Clinical equipment is regularly maintained and calibrated as required. Standard operating procedures and international standards are used where appropriate.

## 2.7 Documentation

Documents related to this work that require archiving will be kept by Eurolens Research for a period of 20 years after completion of the final report. The Sponsor's permission will be sought before the documents are destroyed.

## 2.8 Data collection and analysis

Data collected in this work will be recorded on a custom developed database and an established data trail. Data handling will include export of the study information from the clinical database into spreadsheet format for manipulation, followed by export into a statistical package for analysis. Most clinical data will be entered directly onto the electronic case report form and is considered to be source data.

## 2.9 Study completion

The clinical phase of the study will be considered as complete when all subjects have signed the exit statement.

## 2.10 Confidentiality

All matters related to this work will remain confidential within Eurolens Research, the funding company and any regulatory authority (e.g. Manchester UREC). Eurolens Research will take all reasonable steps to ensure that specific lens-related information is not passed on to study participants unless this is required for clinical management of an adverse event. Personal subject information will not be made available. To cater for this, subjects will only be referred by their unique identity number in the study report. The data activities of Eurolens Research are registered with the data protection officer at The University of Manchester.

## 2.11 Study monitoring

In order to provide quality control and quality assurance as part of this work, the study monitor will:

1. Liaise closely with the Principal Investigator.
2. Monitor and ensure the safety of the subjects.
3. Ensure that the investigation is being conducted according to the protocol.

4. Monitor and review (or oversee review of) the study records to ensure accuracy.
5. Document their observations and make them available to relevant authorised parties (e.g. Manchester UREC).
6. Implement the Eurolens Research clinical monitoring standard operating procedure.

## 2.12 Clinical trial registration

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

# Section 3. Subject management

## 3.1 Visit scheduling

Subjects will be required to attend up to four study visits (three, in the case of the spectacle group). Acceptable date ranges are shown in Table 3. Subjects in the contact lens group may need to attend for more than one 'teach' session.

| Visit | Target | Allowable range |
|---|---|---|
| Initial visit | N/A | N/A |
| 2 week visit (CL group only) | 14 days from initial visit | 10-20 days from initial visit |
| 1 month visit | 30 days from initial visit | 25-35 days from initial visit |
| 2 month visit | 30 days from 1 month visit | 25-35 days from 1 month visit |

**Table 3: Visits and allowable ranges.**

### 3.1.1 Unscheduled visits

Subjects who attend at their own volition, (or as instructed to do so by the investigator) rather than for a scheduled study visit, will be examined and the visit will be classified as 'unscheduled'. Data collected at these visits will be recorded on the clinical study database.

### 3.1.2 Missed visits

Subjects not attending for a visit will be contacted and encouraged to return for assessment. If two consecutive study visits are missed, the subject will be discontinued. It is expected that Eurolens Research personnel will attempt all reasonable means of communication in this event, including corresponding with the subject by letter.

## 3.2 Visit conduct

### 3.2.1 Pre-enrolment

The subject will receive a study-specific information form outlining the study at least 24 hours before the initial visit.

At a suitable time, each subject will be asked to watch a short on-line information presentation detailing study visits and procedures. They will be asked to complete several multiple-choice questions to gauge their understanding of the study. Upon successful completion of these questions, the subject will be booked to attend the initial visit.

### 3.2.2 Initial visit

*Subjects should attend this visit wearing (or having brought along) the spectacles that they use for digital device use (*the visit cannot go ahead if they do not bring their spectacles*)*. They will then be required to sign an informed consent form prior to

enrolment [redacted] A copy of the signed form will be issued to the subject. When the subject has signed the consent form, they are considered to be enrolled on the study.

Subjects will be instructed on the following:

- Lens handling, application and removal, where necessary.
- Use of multipurpose care regimen, where necessary.
- Specific study instructions, such as the importance of not using any other contact lens products.
- General information such as the management of red eyes.

The following procedures will be performed (any ocular measurement procedures outlined below will be carried out on each eye):

1. Details of the ocular history of the subject will be noted (including habitual spectacle details and wear time) This will include recording details about the spectacles to ensure the same pair are worn for the entire study.
2. Details of general health and medications will be recorded.
3. [redacted]
4. The CVS-Q questionnaire will be completed.
5. [redacted]
6. The BVD of the subject's spectacles will be recorded by asking the subject to position the spectacles on their own face (if not already being worn).
7. Focimetry will be carried out on the subject's spectacles to ascertain the prescription of the lenses.
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]

- [redacted]
- [redacted]

12. [redacted]

The presence of any ocular adverse events will be recorded [redacted]

13. The investigator will confirm that the subject satisfies all the inclusion and exclusion criteria. Subjects who fail to meet all the criteria at this time will usually be discontinued and replaced. If in the opinion of the investigator, the subject may be eligible at a later date, the subject may be brought back for up to ONE repeat visit of this type.
14. The subject will be randomised to one of the two treatment groups. The spectacle wearers will be discharged from the study visit at this point, and asked to return for the one-month visit. [redacted]
15. For those assigned to the contact lens group, the study lenses will be fitted and allowed to settle for five minutes or until tearing stops (whichever is the longer).
16. [redacted]

[redacted]

17. [redacted]

18. [redacted]

[redacted]

19. [redacted]

21. Subjects will be trained on contact lens application, removal, solution use and best practice immediately at the end of this visit or at a later date if required. More than one visit is possible for this 'teaching' session if they have problems with handling. Subjects will be dispensed with contact lenses and solution only once the Investigator is satisfied with their ability to successfully apply and remove the lenses.

22. Subjects will be discharged and asked to return for a two-week follow-up visit wearing the Biofinity Energys contact lenses, [redacted] No formal 'building up' of wearing time will take place, [redacted] Some subjects may achieve this on the first day of wear, others may take a few days before they are happy to wear for 8 hours, but all subjects should progress to a minimum of 8 hours per day as soon as they are able. Subjects will also be asked to bring their lens case to the follow-up visit.

### 3.2.3 Two-week visit (contact lens group only)

*Subjects should attend wearing their Biofinity lenses which should have been in situ for at least 2 hours. Subjects who attend without lenses in situ for at least 2 hours will usually be rescheduled.* The following procedures will be performed (any ocular measurement procedures outlined below will be carried out on each eye):

1. Any medical or ocular issues since the last visit will be recorded.
2. [redacted]
3. [redacted]
4. [redacted]
5. The CVS-Q questionnaire will be completed.
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]

[redacted]

10. [redacted]

11. The study lenses will be removed and stored in PureMoist disinfecting solution.
12. A complete biomicroscopic examination will be conducted as outlined in Section 3.2.2 following which the lenses will can be re-applied (after rinsing with saline) or given back to the subject to take home.
13. The subject will be discharged and asked to return for the one month visit wearing the study lenses which need to have been worn for at least 2 hours. Subjects should be asked to wear their lenses for a minimum of 8 hours per day, 5 days per week, and whilst using digital devices for at least 4 hours per day.

### *3.2.4* Visit 3: One month visit

*For the contact lens group, subjects should attend wearing their Biofinity lenses which should have been in situ for at least 2 hours. Subjects who attend without lenses in situ for at least 2 hours will usually be rescheduled.*

*For the spectacle group, subjects should attend wearing (or having brought with them) the spectacles that they have been wearing for digital device use. Spectacles should have been worn for a minimum of 2 hours on the day of the visit.*

For the contact lens group, this visit will be identical to the two week visit except that the contact lenses will be discarded at the end of the visit and they will be provided with a new pair of lenses.

For the spectacle group, the following will take place:

1. Any medical or ocular issues since the last visit will be recorded.
2. Spectacle wearing times since the previous visit will be recorded (hours per day, days per week and comfortable hours per day).
3. [redacted]
4. [redacted]
5. The CVS-Q questionnaire will be completed.
6. [redacted]

7. [redacted]
8. The subject will be discharged and asked to return for the two month visit wearing their spectacles. Subjects should be asked to wear their spectacles for a minimum of eight hours per day, five days per week, and whilst using digital devices for at least four hours per day.

### *3.2.5* Two month visit

This study visit will be identical to the one month visit.

Additionally the following will be carried out:

1. At the final visit (or when the subject is discontinued at an earlier visit) the subject will sign a study exit statement acknowledging that the work is complete, although they may have been asked by the investigator to attend a post-study follow-up visit, and that they should continue to use their lenses (and solutions) as advised, and seek aftercare for their contact lenses. A copy of this signed form will be issued to the subject.
2. The subject will be issued with their payment and discharged.

### 3.2.6 Post-study follow-up visit

In the case of a subject who exits the study with significant clinical signs or symptoms, the investigator must undertake to examine the subject at intervals they determine to be clinically appropriate until the sign or symptom has resolved or returned to a level that is considered to be clinically acceptable. Details from these visits will be recorded on a post-study follow-up visit eCRF.

## 3.3 Monitoring subject compliance

Subjects are required to adhere to the instructions provided during this clinical investigation. This will be confirmed at the study visits by verbal questioning of the subject by the investigator.

## 3.4 Missing, unused and spurious data

The absence of any data will be carefully and critically considered. If appropriate, partial datasets will be included in the final analysis. Any data missing from a subject visit will be outlined in the report by indicating the number of subjects included for each analysis. Data that are unused or considered to be spurious will be detailed and discussed in the report.

# Section 4. Study co-ordination

## 4.1 Document processing

All case report forms will be processed and evaluated by Eurolens Research, who will produce the final report with full statistical analysis. A draft report will be sent to the Industrial Contact Person in order to make comments and ask for re-drafts. If no comments are received from the Industrial Contact Person within eight weeks, a final report will be released with a separate document control page (in duplicate), requesting the Industrial Contact Person to sign both copies, one to keep and the other to be returned to Eurolens Research.

## 4.2 Disclosure

All matters relating to this clinical study are confidential and should only be disclosed to relevant authorised parties. More precise details relating to disclosure are outlined in the Research Agreement. None of the investigators involved in this work owns equity in the funding company.

## 4.3 Personnel

**Industrial Contact Person**