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Centre for Ocular Research & Education

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Protocol

COMPARISON OF TEAR EVAPORATION RATE WITH DAILIES TOTAL1 AND BIOTRUE ONEDAY (MALTESE)

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CORE protocol number: P/683/19/CORE

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DOCUMENT CHANGE HISTORY

Version date	Author	Description of change(s)
25Jun2019	[redacted]	Original protocol
24Jul2019	[redacted]	[redacted] Section 4.2.3 “11. Has a wearable pair of spectacles.” has been added as an inclusion criterion. Section 4.4.3 updated to clarify that the participant will apply the petroleum jelly. Section 4.4.3 and 4.4.4 updated to clarify that the participant will remove the petroleum jelly. Section 4.5.11: • Removed “The syringe also be wiped with an alcohol wipe prior to use.” • Added “A new sterile, syringe will be used for each participant.” Section 6 added “Participants may experience temporary discomfort including: blurred vision and light sensitivity.”

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Confidentiality

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Disclaimer

This study will be conducted for research purposes only and is not intended to be used to support safety and efficacy in a regulatory submission.

1 INTRODUCTION

There are estimated to be more than 140 million contact lens (CL) wearers throughout the world and approximately 50-75% of CL wearers report suffering from symptoms of irritation while wearing their lenses.[1] CL-related dryness is a leading cause of CL discontinuation[1] [2] and two factors reportedly related to CL dryness include a rapid pre-lens tear film thinning time and lenses with a higher nominal water content.[3]

Evaporimetry is a non-invasive method of assessing the rate of evaporation of the tear film from the front surface of the eye. At present, there is only one commercial evaporimeter, the Eye-VapoMeter (Delfin Technologies Ltd., Finland), available for clinical use. The 2017 TFOS DEWS II Tear Film report noted that there is currently a lack of reliable, commercially available evaporimeters. The report stressed that the development of evaporimeters that can be used in a clinical setting under a variety of temperatures and humidities would be extremely useful.[4]

The Eye-VapoMeter was initially designed as a dermatological device to measure the rate of skin evaporation. The device was modified by incorporating an eye cup from a swimming goggle onto the base of the instrument and was validated for ocular use in 2014.[5]

All other evaporimeters previously described in the literature have only been used within a research setting. To our knowledge, there has only been one previous evaporimeter which was capable of binocularly measuring the tear evaporation rate (TER). Tsubota and Yamada reported on the development of an evaporimeter capable of simultaneously measuring both eyes in 1992.[6] The evaporimeter consisted of a modified swimming goggle which had a 44 ml closed cylinder attached to each side of the goggle. The cylinders were needed to accommodate the large size of the sensors, which were used to record the temperature and relativity humidity.

To overcome various problems associated with the Eye-VapoMeter and the Yamada/Tsubota evaporimeter, a novel, prototype goggle-based evaporimeter has been designed to simultaneously measure TER from both eyes at the same time. The benefit of a simultaneous TER measurement is less chair time for both the patient and practitioner.

The prototype evaporimeter incorporates a small 2.5 x 2.5 mm^2 temperature and humidity sensor into each lens of a swimming goggle, which eliminates the need to alter the original design of the goggle. The sensors sample the humidity and temperature 4 times per second and are positioned closer to the eye than inside the Eye-VapoMeter or the Yamada/Tsubota evaporimeter. The location of the sensor can provide a more accurate measurement of the humidity at the ocular surface by reducing the amount of extraneous air volume within the goggle.

Due to the relative lack of previously published research investigating evaporimetry and CLs, the purpose of this pilot study is to compare the effect of DAILIES TOTAL1, a low water content silicone hydrogel lens, and Biotrue ONEday, a high water content hydrogel lens, on TER. The study will also serve to validate the novel, in-house developed evaporimeter.

2 OBJECTIVES

The objective of the study is to compare the rate of tear evaporation, measured with a novel evaporimeter, before and after DAILIES TOTAL1 and Biotrue ONEday CLs are worn in symptomatic and asymptomatic contact lens wearers.

The primary outcome variable for this study are the slopes calculated from the change in relative humidity over time.

Other variables of interest include:

- Contact lens dry eye questionnaire-8 (CLDEQ-8) score
- Comfort (subjective rating)
- Dryness (subjective rating)
- Non-invasive break up time
- Lipid layer thickness (Tearscope, LipiView II)
- Ocular surface area (mm^2)
- Volume inside the goggle (cm^3)

3 HYPOTHESIS

The study hypothesis is that there will be a higher rate of tear evaporation with CL wear compared to when CLs are not worn.

There will also be a significant difference in the rate of tear evaporation of DAILIES TOTAL1 (DT1) and Biotrue ONEday (BOD) after a minimum of 6 hours of CL wear.

There will also be a higher rate of tear evaporation in symptomatic contact lens wearers compared to asymptomatic lens wearers.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

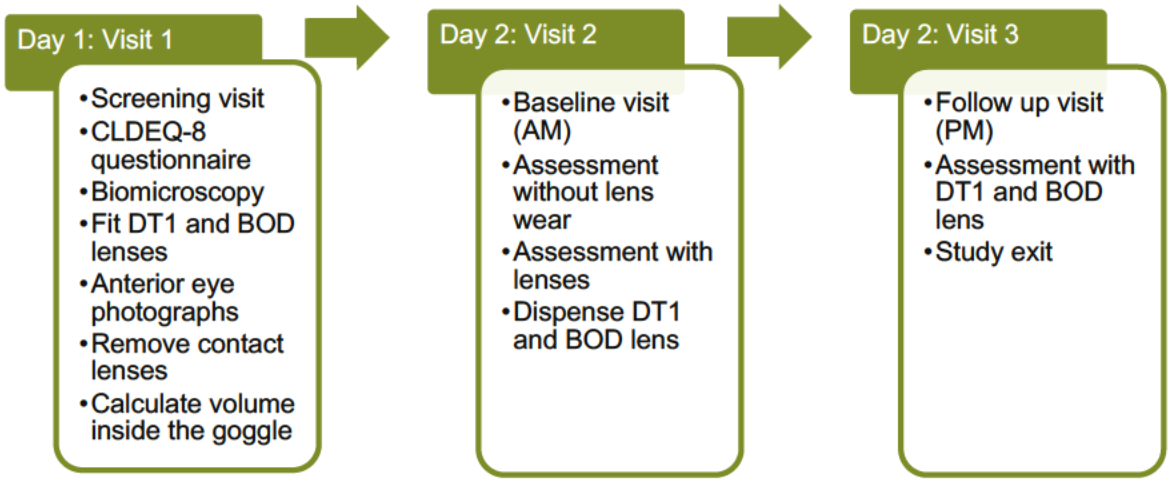
This study is a prospective, double-masked (investigator and participant), contralateral, non-dispensing study. Each participant will be randomized to wear DT1 in one eye and BOD in the fellow eye. Both lenses will be worn on a daily wear basis. This study will involve 3 scheduled visits over 2 days.

Visit 1: Screening and contact lens fitting visit

Visit 2: Baseline dispensing visit with BOD and DT1 lenses (morning visit)

Visit 3: Follow up visit with BOD and DT1 lenses (afternoon visit)

Visit 2 (baseline visit) and Visit 3 (follow up visit) will be conducted on the same day. There will be 5.5 hours ± 30 minutes between Visit 2 and Visit 3, during which time participants are not required to remain at the School of Optometry & Vision Science.



4.1.2 RANDOMIZATION

A randomization schedule will be generated using a web-based program: (www.randomization.com). Participants will be randomized to the type of contact lens to be worn in each eye at Visit 2. A separate randomization will be generated for symptomatic and asymptomatic participants. The final study randomization schedule will be generated by CORE's Database Administrator, and provided to the research assistants for the study. Study investigators will remain masked to the randomization schedule until the interim data analysis. Study investigators will be granted access to the randomization schedule for the first 10 symptomatic and 10 asymptomatic participants in order to conduct the interim data analysis. Following

calculation of the sample size required to complete the study, study investigators will remain masked to the remainder of the randomization schedule until the study is completed and the database is locked.

4.1.3 MASKING

Participants will be masked to the brand of contact lens worn in each eye at Visit 2 and Visit 3. In order to mask the participant, a research assistant will transfer the lenses and blister pack solution directly from the blister packs and will place them in a contact lens cup. The investigator will be masked as much as possible; however, it may not be possible to fully mask the investigator, because identifying lens markings may be visible during the biomicroscopy examination.

4.2 STUDY POPULATION

4.2.1 SAMPLE SIZE CALCULATION

Because this is a pilot study, a sample size calculation has not been completed. An interim data analysis will be undertaken after 20 participants (10 symptomatic and 10 asymptomatic) have completed the study. The results of the interim data analysis will be used to calculate a sample size using G*Power.

A p-value of < 0.05 will be considered statistically significant.

4.2.2 NUMBER OF PARTICIPANTS

Up to 50 participants will be screened using CORE records and advertising approved by the UW Office of Research Ethics. Up to 50 participants will be dispensed/randomized with study products, with a target of at least 10 symptomatic and 10 asymptomatic participants completing the study. Informed consent will be obtained for all participants prior to their enrolment in the study.

4.2.3 INCLUSION AND EXCLUSION CRITERIA

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

1. Is at least 17 years of age and has full legal capacity to volunteer;
2. Has read and signed an information consent letter;
3. Is willing and able to follow instructions and maintain the appointment schedule;
4. Has worn soft contact lenses for a minimum of 6 months;
5. Currently wears soft contact lenses for at least 4 days per week and 8 hours per day;
6. Has an acceptable fit and comfort with both study contact lenses in the powers available;
7. Has $\leq$1.00DS difference between eyes in their habitual contact lenses;

8. Is willing to be awake for at least 2 hours before visit 2;
9. Is willing to not wear eye makeup on the day of visit 2 and 3;
10. Is willing to not use eye drops or artificial tears on the day of visits 1, 2, and 3;
11. Has a wearable pair of spectacles.

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

1. Is participating in any concurrent clinical or research study;
2. Has any known active* ocular disease and/or infection;
3. Has a systemic condition that in the opinion of the investigator may affect a study outcome variable;
4. Is using any systemic or topical medications that in the opinion of the investigator may affect a study outcome variable;
5. Has known sensitivity to sodium fluorescein dye;
6. Is pregnant, lactating or planning a pregnancy at the time of enrolment (by verbal confirmation at the screening visit);
7. Is aphakic;
8. Has undergone refractive error surgery;
9. Has a known sensitivity to petroleum jelly (Vaseline);
10. Has epilepsy and/or a sensitivity to flashing lights;
11. Wears toric contact lenses;
12. Has any physical impairment that would interfere with holding the evaporimeter;
13. Has taken part in another research study within the last 14 days.

* For the purposes of this study, active ocular disease is defined as infection or inflammation which requires therapeutic treatment. Mild (i.e. not considered clinically relevant) lid abnormalities (blepharitis, meibomian gland dysfunction, papillae), corneal and conjunctival staining and dry eye are not considered active ocular disease. Neovascularization and corneal scars are the result of previous hypoxia, infection or inflammation and are therefore not active.

4.2.4 REPEATED SCREENINGS

In some circumstances a repeated screening may need to be scheduled. Examples include, but are not limited to:

1. Incomplete information available at time of screening to determine eligibility (e.g. current lens brands worn, history from current eye care practitioner etc.)
2. Study procedures unable to be completed in time scheduled for visit;

3. Study products not available at the time of the screening visit;
4. A transient health condition which may affect the eye(s) (e.g. a common cold, active allergies, fatigue etc;)
5. The short term use of medications (e.g. antibiotics, antihistamines etc.)
6. Reassessment of baseline ocular conditions (e.g. corneal and/or conjunctival staining, scars etc.)

The maximum total number of screenings permitted will be 3 (i.e. 2 repeated screenings are allowed).

4.3 STUDY MATERIALS

4.3.1 LENSES

Details of the study lenses are shown in Table 1.

Table 1: Lens parameters to be used in this study

Lens	Biotrue ONEday	DAILIES TOTAL1
Manufacturer	Bausch & Lomb Inc.	Alcon Canada Inc.
Material	nesofilcon A	delefilcon A
HC licence #	89630	87774
EWC (%)	78%	core 33%, surface ≥ 80%
Dk/t at -3.00D	42	156
Sphere power (D)	+0.50 to +6.00 (in 0.25 steps) -0.50 to -6.00 (in 0.25 steps) -6.50 to -9.00 D (in 0.50 steps)	+0.50 to +6.00 (in 0.25 steps) -0.50 to -6.00 (in 0.25 steps) -6.50 to -9.00 (in 0.50 steps)
Base curve (mm)	8.6	8.5
Diameter	14.2	14.1

4.3.2 LENS CARE SYSTEM

No contact lens care system is required for this study as all the lenses are daily disposable lenses designed to be worn for a single day and then discarded.

Lenses will be discarded after being worn at the screening visit (Visit 1) and at the end of the follow up visit (Visit 3).

4.3.3 REWETTING DROPS & SALINE

Participants will not be encouraged to use rewetting drops; however, those who habitually use rewetting drops will be allowed to continue using their normal drops, except for on the day of the screening (Visit 1) and on the day of Visits 2 and 3. Rewetting drop use will be recorded at each visit. In the event of an adverse event, rewetting drops may be given to participants.

Saline solution may be used to rinse residual sodium fluorescein from the eyes following corneal staining assessment.

The use of saline for rinsing the CL prior to insertion is permitted, if necessary. If initial CL discomfort is reported after a lens has been inserted, a CL may be removed, rinsed with saline, and re-inserted.

4.3.4 ORDERING CONSUMABLES

Study products will be obtained through commercial sources.

4.3.5 DISPOSING OF CONSUMABLES

Lenses worn at the scheduled visits will be collected from the participants and disposed of according to UW guidelines.

4.3.6 PRODUCT ACCOUNTABILITY

Accountability logs will be kept to include the number of lenses dispensed. All products dispensed to participants will be recorded in the study binder.

4.3.7 CONTACT LENS DISPENSING

At Visit 1, participants will insert the CLs directly from the labelled blister pack in order to ensure an acceptable lens fit.

At Visit 2, the CLs will be provided to the participant after being transferred, complete with the blister pack solution, to a CL cup; in order to maintain participant and investigator masking.

The use of saline for rinsing the CL prior to insertion or just after insertion is permitted, if necessary. Saline will not be dispensed during the study.

4.4 SCHEDULED AND UNSCHEDULED VISITS

This study has a total of 3 study visits, including the screening visit, including:

- Visit 1: Screening and fitting of study lenses,
- Visit 2: Baseline measurements and dispensing of study lenses,
- Visit 3: Follow-up visit with study lenses on the same day as Visit 2 and study exit.

4.4.1 STUDY VISITS

The study has a total of 3 study visits, including the screening visit. Visit 2 and Visit 3 will occur on the same day and will be scheduled up to 14 days after the screening visit (Visit 1). The total time

commitment for the scheduled visits is 4 hours of active participation. The summary of visit codes is shown in Table 2.

Table 2: Summary of visit codes

Visit #	Visit code	Study Day	Visits	Duration (hours)
1	V1 (V1-R1, V1-R2 for re-screen ng)	1	Screen ng and f tt ng	1.5
2	2	2	Base ne & d spense study enses V s t 2 w be schedu ed up to 14 days after V s t 1	1.5
3	3	2	Fo ow up w th study enses & study ex t V s t 3 w be schedu ed 5.5 hours ± 30 m nutes after the comp et on of V s t 2	1

4.4.2 VISIT 1: SCREENING

All participants who sign the informed consent letter will be assigned a study ID number. The investigator will determine participant eligibility using the inclusion and exclusion criteria. Ineligible participants will be discontinued from the study. The procedures to be performed are outlined below:

- Participants will attend the screening visit having not worn their habitual contact lenses on the day of the visit.
- Participants will attend the screening visit having not used any eye drops or artificial tears on the day of the visit.
- The participant will be required to read and sign an Informed Consent Form prior to enrollment. When the participant has signed the consent form, the participant will be considered to be enrolled in the study.
- Participant demographics and medical history (age, sex, medical conditions, medications, allergies)
- Contact lens history (own lens information and wearing time)
- Contact lens dry eye questionnaire-8 (CLDEQ-8)
- Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with spectacles or spectacle refraction.
- Assessment of meibomian gland expression
- Lid margin assessment
- Slit lamp biomicroscopy
- The investigator will confirm that the participant meets the eligibility specifications set out in the inclusion criteria and exclusion criteria and is eligible to continue with the remainder of the screening visit.

- Trial fitting of both study lenses will be done:
    - The lenses will be inserted by the participant directly from the blister pack based on their current contact lens power.
    - The contact lenses will be allowed to settle for 10 minutes.
    - Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with the study lenses.
    - Spherical over-refraction
    - Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with the study lenses and over-refraction.
    - Contact lens fit will be assessed.
- Anterior eye photographs of each eye will be taken with a slit lamp camera.
- Participants will practice evaporimetry measurements.
- Removal of study lenses.
- Measurement of volume within the goggle.
- Slit lamp biomicroscopy (safety check)
- Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with spectacles or spectacle refraction.
- The investigator will confirm that the participant meets the eligibility specifications set out in the inclusion criteria and exclusion criteria and is eligible to continue with the study.

4.4.3 VISIT 2: BASELINE AND DISPENSING VISIT

- Participants will attend the visit having been awake for at least 2 hours.
- Participants will not have worn any contact lenses, used any eye drops or artificial tears, or worn any eye makeup on the day of the visit. Participants who have worn lenses, used eye drops, used artificial tears, or worn eye makeup on the day of the visit will be rescheduled.
- Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with spectacles or spectacle refraction.
- Slit lamp biomicroscopy using white light.

The participant will be assigned a randomization ID in order to determine which type of CL will be inserted into each eye.

Participants will be required to adapt to the room environment for at least 15 minutes prior to reporting subjective monocular ratings and performing baseline evaporimetry measurements. The

participant will apply thin layer of petroleum jelly will be applied to the skin surrounding the eye using a cotton tipped applicator to minimize the amount of evaporation from the skin.

- The participant will be asked to give subjective monocular ratings for:
  - Comfort
  - Dryness
  - Burning or stinging
- Baseline evaporimetry measurements without contact lenses
- Non-invasive pre-ocular tear film break up time (Tearscope)
- Lipid layer thickness (Tearscope)
- Lipid layer thickness (LipiView II)
- Evaporimetry measurements will be repeated at least 15 minutes after the initial baseline measurement.
- Non-invasive pre-ocular tear film break up time (Tearscope)
- Lipid layer thickness (Tearscope)
- Lipid layer thickness (LipiView II)
- The participant will wipe away petroleum jelly from skin surrounding the ocular surface using a tissue.
- Contact lenses will be given to the participants in a masked manner (Section 4.3.7).
- The study contact lenses will be inserted by the participant.
- The lenses will be allowed to settle for at least 15 minutes.
- The participant will apply a thin layer of petroleum jelly will be applied to the skin surrounding the eye using a cotton tipped applicator to minimize the amount of evaporation from the skin.
- The participant will be asked to give subjective monocular ratings for:
  - Comfort
  - Dryness
  - Burning or stinging
- Baseline evaporimetry measurements with contact lenses.
- Non-invasive pre-lens tear film break up time (Tearscope)
- Lipid layer thickness (Tearscope)
- Lipid layer thickness (LipiView II)
- Contact lens fit will be assessed.

- Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with contact lenses.
- The participant will wipe away petroleum jelly from surrounding the ocular surface using a tissue.

Participants will continue to wear the study lenses and will be advised not to use any eye drops or eye makeup. Participants will be instructed to return to CORE in 5.5 hours ± 30 minutes for their next visit.

4.4.4 VISIT 3: FOLLOW UP & STUDY EXIT

Participants will attend the visit having not used any eye drops or eye makeup on the day of the visit.

- Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination.
- Contact lens fit will be assessed.

Participants will be required to adapt to the room environment for at least 15 minutes prior to reporting subjective monocular ratings and performing evaporimetry measurements. The participant will apply thin layer of petroleum jelly will be applied to the skin surrounding the eye using a cotton tipped applicator to minimize the amount of evaporation from the skin.

- The participant will be asked to give subjective monocular ratings for:
  - Comfort
  - Dryness
  - Burning or stinging
- Evaporimetry measurements with contact lenses. Evaporimetry measurements will not be taken until the study lenses have been worn for a minimum of 6 hours.
- Non-invasive pre-lens tear film break up time (Tearscope)
- Lipid layer thickness (Tearscope)
- Lipid layer thickness (LipiView II)
- The participant will wipe away petroleum jelly from the skin surrounding the ocular surface using a tissue.
- Contact lens removal.
- Slit lamp biomicroscopy.
- Exit monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with spectacles or spectacle refraction.

Study Exit

- The study exit form will be completed when a participant exits the study. This will occur either at study completion, or if the participant is discontinued from the study at another time. A study exit form must be completed for all participants who have been given a study number. If in the opinion of the investigator post-study follow-up visits are required, the exit form will be completed after the last follow-up visit.
- The participant will be discharged and will sign the study completion forms and receive remuneration for participating in the study.

4.4.5 UNSCHEDULED VISITS

An unscheduled visit is defined as an interim visit requested by the participant or investigator due to an unanticipated problem. Data recorded at these visits will be entered into the database. Only relevant and applicable unscheduled visit information will be included in the final report as deemed necessary by the lead investigator.

4.5 STUDY PROCEDURES

Table 3 summarizes the visits and procedures for the study.

Table 3: Summary of procedures to be conducted at scheduled visits

Procedure	Visit 1	Visit 2	Visit 3	Instrument/application
Informed consent (screen ng)	√			Invest gator
Demograph cs	√			Invest gator
Contact ens h story	√			Invest gator
Med ca h story	√	√	√	Invest gator
CLDEQ-8	√			Quest onna re (paper)
VA w th spectac es or refract on	√	√	√	V sua acu ty chart
Me bom an g and assessment	√			Me bom an G and Eva uator (ower d)
L d marg n assessment	√			S t amp
S t amp b om croscopy (w th sta n ng)	√		√	S t amp
Conf rmat on of nc us on/exc us on cr ter a	√			Invest gator
Tr a f tt ng of study enses	√			Invest gator
VA w th contact enses	√	√	√	V sua acu ty chart

Procedure	Visit 1	Visit 2	Visit 3	Instrument/application
Over-refract on	√			Phoropter
Lens f t assessment	√	√	√	S t amp
Anter or eye photography	√			S t amp and camera
Evapor metry pract ce	√			Evapor meter
Remova of contact enses	√		√	Part c pant
Measurement of vo ume ns de the gogg e	√			Mod f ed sw mm ng gogg e
S t amp b om croscopy (safety w th sta n ng)	√			S t amp
S t amp b om croscopy (wh te ght)		√		S t amp
Subject ve assessment (comfort, dryness, burn ng/st ng ng)		√	√	Quest onna re (paper)
App cat on of petro eum je y		√	√	Part c pant
Evapor metry		√	√	Prototype evapor meter
Non- nvas ve break up t me		√	√	Kee er Tearscope
L p d ayer th ckness		√	√	Kee er Tearscope, TearSc ence L p V ew II
Remova of petro eum je y		√	√	Part c pant
Study comp et on and ex t			√	N/A

4.5.1 DEMOGRAPHICS

Demographic information will be obtained from the participant, including age and sex.

4.5.2 CONTACT LENS HISTORY

Information will be obtained from the participant, including the type of contact lenses they currently wear, the solution that they use, and how often they wear their lenses.

4.5.3 MEDICAL HISTORY

At the screening visit, medical history questions to determine any current medications, allergies and relevant medical conditions will be asked and documented. At subsequent visits, participants will be asked about changes in their medication or medical condition(s).

4.5.4 CONTACT LENS DRY EYE QUESTIONNAIRE (CLDEQ-8)

The CLDEQ-8 is a dry eye questionnaire that asks the participant to reflect and rate their symptoms of eye discomfort and dryness over the past two weeks. A higher composite score indicates more severe dryness and the range is 0-37. A score of $<$12 will be considered asymptomatic and a score $\geq$12 will be symptomatic.

4.5.5 LOGMAR VISUAL ACUITY

Distance logMAR visual acuity will be measured using high contrast computer-generated acuity charts in high illumination room lighting. Participants will be asked to read letters, which progressively decrease in size on a computer screen at a viewing distance of 6 meters, with their habitual glasses/spectacle refraction or study contact lenses.

4.5.6 MEIBOMIAN GLAND ASSESSMENT

Participants will be seated at a slit lamp biomicroscope with the magnification set to 10x or 16x. The participant will be asked to look up and away from their nose. The meibomian glands will be manually expressed using the MG Evaluator (TearScience/J&J). The MG Evaluator will be depressed halfway to apply a pressure of 1.2 g/mm^2 to three separate areas (nasal, central, temporal) on the lower eyelid just below the lash line and angled down approximately 15 to 45 degrees. Five consecutive glands in each area will be assessed for expressibility as follows: 0: no secretion (including capped orifices), 1: inspissated (semi-solid, toothpaste like), 2; colored/cloudy liquid, 3: clear liquid oil. The results for each eye will be summed (Meibomian Gland Score).

4.5.7 LID MARGIN ASSESSMENT

The participant will be seated at a slit lamp biomicroscope.

Vascularity of the margin (erythema)

The vascularity of the lid margin will be graded (0-4 scale; 0: none, 1: minimal, 2: mild, 3: moderate, 4: severe).

Amount of lash loss

The amount of lash loss will be assessed (0-4 scale; 0: none, 1: minimal, 2: mild, 3: moderate, 4: severe).

Lid margin edema

The presence or absence of lid margin edema will be recorded.

Lid margin telangiectasia

Lid margin telangiectasia will be graded (0-4 scale, 0: none; 1: single telangiectasia; 2: 2 to 5 telangiectasia; 3: >5 telangiectasia; 4: severe-entire lid involvement).

Tear film debris

The presence or absence of tear film debris will be recorded.

4.5.8 SLIT LAMP BIOMICROSCOPY

A slit lamp biomicroscopy examination will be conducted to assess anterior segment ocular health. Ocular findings will be graded using the Efron grading scale (0-4, 0.5 steps – unless otherwise stated):

External adnexa anomalies

The presence or absence of external adnexa anomalies will be recorded. If adnexa anomalies are detected, the anomaly will be described.

Bulbar and limbal hyperemia

The redness of the bulbar and limbal conjunctiva of both eyes will be assessed using the Efron Grading scale (0 to 4, 0.5 steps).

Scars or other corneal observations

The presence or absence of scars or other corneal observations will be recorded. If scars or other corneal observations are detected, the finding(s) will be described.

Infiltrates

The presence or absence of infiltrates will be recorded. If present, the number and location will be recorded. The size (diameter in mm) and depth of the largest infiltrate (0-4 scale, 1 step) in the central, mid-periphery and periphery will be noted.

Endothelium abnormalities:

The presence or absence of endothelium abnormalities will be recorded. If endothelium abnormalities are detected, the finding(s) will be described.

Anterior chamber

The presence or absence of anterior chamber reaction will be recorded. If an anterior chamber reaction is detected, the finding(s) will be described.

Other abnormalities

The presence or absence of other abnormalities will be recorded. If other abnormalities are detected, the finding(s) will be described.

Corneal and conjunctival staining and indentation

A sodium fluorescein strip, wetted with a few drops of saline, will be applied to the superior bulbar conjunctiva of both eyes. Corneal staining type will be graded using the Efron scale (0 to 4, 0.5 steps), staining extent and depth will be graded on a (0 to 4 scale, 1 step) while viewing with cobalt blue light and Wratten filter (if available). Conjunctival staining and indentation will be graded using a 0 to 4 scale (0.5 steps), with larger values indicating increasing severity.

Mucin ball impressions

The number of mucin ball impressions will be recorded.

Palpebral conjunctival hyperemia and papillae (roughness)

The redness and roughness of the upper and lower eyelids will be assessed using the Efron scale (0 to 4, 0.5 steps).

4.5.9 CONTACT LENS FITTING

The acceptability of the fit of the study lenses will be assessed using a slit lamp biomicroscope after the lenses have settled for at least 10 minutes. Lens fit (centration, movement, limbal coverage, tightness/push up test, overall fit) will be determined to be either acceptable or unacceptable. Lens deposits will be recorded as present/absent. The participants will be asked to report if the lenses are subjectively comfortable (yes/no) at the screening visit.

4.5.10 ANTERIOR EYE PHOTOGRAPHS

The participant will be seated at a Zeiss slit lamp attached to a Canon EOS 60D digital camera. A photograph of each eye will be taken at 5x magnification with additional external illumination provided by a Canon Macro Twin Lite flash. The participant will hold a ruler underneath each eye while the photographs are taken. The ruler will serve as a calibration reference when the images are analysed with ImageJ in order to determine the size of the ocular surface in mm^2. The ruler will be cleaned with an alcohol wipe prior to being given to each participant.

4.5.11 MEASUREMENT OF VOLUME INSIDE THE GOGGLE

The participant will be seated in a consulting chair and will be asked to rest their head on the headrest. A pair of swimming goggles (Arena Zoom X-Fit), which are the same make and model as the prototype evaporimeter, will be used. The swimming goggle has been modified by drilling a small hole into the top of each lens. The participant will be asked to place the goggle over both eyes and to tighten the strap. A plastic, needleless syringe, with a 200 μl pipette tip attached to the end of the syringe, will be filled with saline (Bausch & Lomb Sensitive Eyes Saline Plus). Participants will be asked to keep their eyes closed while saline is added to the goggle. Saline will be added to each swimming goggle until the goggle has been filled with saline. The amount of saline added to each goggle will be recorded in milliliters. When the goggle is ready to be removed, the participant will be advised to tilt their head forward and continue to keep their eyes closed. A plastic tub will be placed below the participant's face and paper towels will be placed around the goggle to catch any saline that may spill out of the goggle. When the goggle has been removed, the participant will be advised to wipe their face with a paper towel while their eyes are kept closed. The swimming goggle will be cleaned with an alcohol wipe prior to use on each participant. A new sterile, syringe will be used for each participant. New saline and a new pipette tip be used to fill each goggle.

4.5.12 SLIT LAMP BIOMICROSCOPY (SAFETY VARIABLE)

The participant will be seated at a slit lamp at the following will be assessed in both eyes for:

External adnexa anomalies

The presence or absence of external adnexa anomalies will be recorded. If adnexa anomalies are detected, the anomaly will be described.

Bulbar and limbal hyperemia

The redness of the bulbar and limbal conjunctiva of both eyes will be assessed using the Efron Grading scale (0 to 4, 0.5 steps).

Scars or other corneal observations

The presence or absence of scars or other corneal observations will be recorded. If scars or other corneal observations are detected, the finding(s) will be described.

Infiltrates

The presence or absence of infiltrates will be recorded. If present, the number and location will be recorded. The size (diameter in mm) and depth of the largest infiltrate (0-4 scale, 1 step) in the central, mid-periphery and periphery will be noted.

Corneal and conjunctival staining and indentation

A sodium fluorescein strip, wetted with a few drops of saline, will be applied to the superior bulbar conjunctiva of both eyes. Corneal staining type will be graded using the Efron scale (0 to 4, 0.5 steps), staining extent and depth will be graded on a (0 to 4 scale, 1 step) while viewing with cobalt blue light and Wratten filter (if available). Conjunctival staining and indentation will be graded using a 0 to 4 scale (0.5 steps), with larger values indicating increasing severity.

4.5.13 APPLICATION OF PETROLEUM JELLY

Petroleum jelly will be removed from the original container using a cotton tipped applicator and placed in a new paper cup for each participant. Another cotton tipped applicator will be given to each participant to apply thin layer of petroleum jelly to the skin surrounding the eye using a mirror. A new cotton tipped applicator and paper cup will be used for each application. Any remaining petroleum jelly will be disposed of according to UW guidelines.

4.5.14 REMOVAL OF PETROLEUM JELLY

To remove petroleum jelly from the skin, the participant will close their eyes and wipe with a tissue in a nasal to temporal direction, with extra care being paid wiping near the lid margin to avoid contaminating the tear film or contact lenses.

4.5.15 SUBJECTIVE COMFORT RATINGS

Participants will be asked to fill a numerical analog scale for comfort, dryness, and burning or stinging for each eye on a 0-100 scale:

- At Visit 2, before & 15 minutes after lens insertion
- At Visit 3, after at least 6 hours of contact lens wear.

4.5.16 EVAPORIMETRY

The participant will be seated at an adjustable height table and will place their elbows on the table. The participant will hold a pair of modified swimming goggles (Figures 1A and 1B) over their eyes for 20 seconds while their eyes are open. The participant will be prompted to blink every 3 seconds during the measurement using a metronome (https://www.youtube.com/watch?v=9ypeNJJeKIs). The goggle will be removed and ventilated in front of a fan until the relative humidity returns to

baseline levels. The goggle will then be placed over the eyes for 20 seconds while they are closed to measure the evaporation rate from the skin. Three consecutive measurements of open eye and closed eye measurements will be taken. Recordings of the temperature and relative humidity during the measurement will be saved as a text file and images of the temperature and humidity versus time plotted as a graph will be saved as a png file. The rate of tear evaporation will be calculated from slope derived from the change in relative humidity over time. The evaporation rate from the ocular surface will be calculated by subtracting the evaporation rate of closed eye from the evaporation rate of the open eye. The average of three ocular surface evaporation rates will be calculated for each eye.

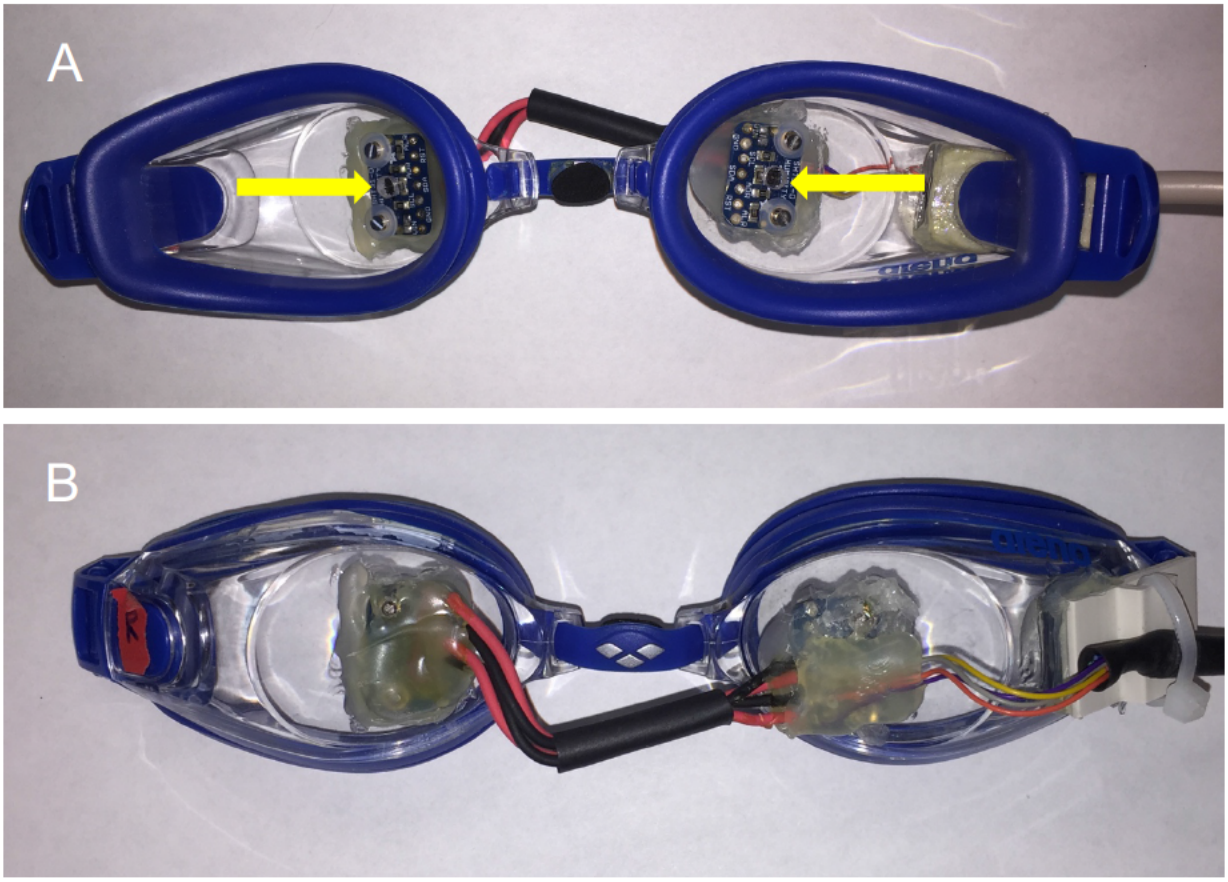


Figure 1: (A) Evaporimeter with arrows showing the location of the temperature/humidity sensors in the swimming goggle. (B) View of the front of the evaporimeter.

4.5.17 NON-INVASIVE TEAR FILM BREAK UP TIME (NITBUT) (KEELER TEARSCOPE)

The participant will be seated at a slit lamp and a diffuse white light will be shone onto the participant's eye without a grid insert. The Keeler Tearscope is a hand-held device with projects a diffuse white light onto the surface of the eye to allow the investigator to better see the lipid layer

of the tear film while the participant is sitting behind the slit lamp. This device is not computerized and does not generate data. The timer on the instrument will be used to measure the non-invasive break-up time. The non-invasive break-up time will be recorded as the time taken after a blink until the appearance of the first dark spot.[7] Three measurements will be taken from each eye and the average value will be calculated for each eye.

4.5.18 LIPID LAYER THICKNESS (KEELER TEARSCOPE)

The participant will be seated at a slit lamp and a diffuse white light will be shone onto the participant's eye. Lipid layer thickness will be graded according to the interference pattern observed based on Guillon and Guillon's classification system[7] (open meshwork, closed meshwork, wave, amorphous, colour fringe, and other).

4.5.19 LIPID LAYER THICKNESS (TEARSCIENCE LIPIVIEW II)

The participant will be seated at the LipiView II instrument which will image and compute the lipid layer thickness (average, minimum, maximum) of the tear film. Prior to the commencement of this test, no history of seizures or discomfort with rapidly blinking lights will be confirmed.

5 MONITORING PROTOCOL ADHERENCE

Guidelines to be included on adherence to visit windows and windows around other data collection points (i.e. subjective ratings) will be monitored by CORE. Deviations from the windows described in the protocol will be reported in the study report. Major protocol deviations will be reported to the University of Waterloo's Office of Research Ethics (ORE) within 7 days of becoming aware of them (as per ORE's guidelines).

6 POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

This is a minimal risk study because of the use of marketed products and standard optometric assessments with two investigational, non-invasive devices (the prototype evaporimeter and the modified swimming goggles used to measure volume).

Contact lenses in this study will be worn on a daily wear basis, for approximately 6 to 7 hours. Adverse events and/or complications in daily wear of soft contact lenses can occur (eg: inflammation and infection). When contact lenses are worn on a daily wear basis there is a small risk of an adverse event compared to not wearing contact lenses. When contact lenses are worn on an extended wear basis, there is a significantly increased risk of an adverse reaction compared with wearing contact lenses on a daily wear basis.

Additionally, it is possible that participants may experience temporary discomfort associated with the study procedures (saline)/products/devices including: burning and stinging, blurred vision, sandiness or grittiness, light sensitivity, dryness, itching, crusty eyes and foreign body sensation.

A dye (fluorescein) normally used for eye exams is being used in this study. Although rare, it is possible that participants may have an allergic reaction to the dye. This could cause discomfort to their eye.

Routine clinical procedures including visual acuity, anterior ocular health assessment, and contact lens fitting will be used.

One clinical procedure (evaporimetry) will be conducted with an investigational device consisting of a pair of modified swimming goggles containing a temperature and humidity sensor embedded in each lens of the goggle. This procedure poses minimal risk to the participants as the device is does not touch the eye and the portion of the goggle which will come in contact with the skin surrounding the eye will be cleaned with alcohol wipes between each use. Participants may experience temporary discomfort associated with petroleum jelly including; burning, stinging, irritation, blurred vision, and foreign body sensation.

One clinical procedure (measurement of volume inside the goggle) will be conducted with an investigational device consisting of a pair of modified swimming goggles containing small hole inserted into the top of each lens. This procedure poses minimal risk to the participants as the device is does not touch the eye and the portion of the goggle which will come in contact with the skin surrounding the eye will be cleaned with alcohol wipes between each use. Commercially available saline designed for use with the eyes will be inserted into the goggle. Participants may experience temporary discomfort associated with saline including; burning, stinging, irritation, blurred vision, and foreign body sensation.

One of the instruments in this study uses rapidly blinking lights to image the tear film. Participants will be asked to inform the investigator if they have a history of discomfort and seizures due to rapidly blinking lights. Participants may experience temporary discomfort including: blurred vision and light sensitivity.

Participants may not benefit directly from taking part in this study. Information from this study may help researchers come up with new devices to help others in the future. This study may help CORE to better understand the performance of the products being used in this study.

7 ADVERSE EVENTS

See CORE SOP012_v02 for a description of all adverse events, including management and reporting.

A number of conditions may result in temporary suspension until resolution. These include corneal infiltrates, corneal staining, limbal injection, bulbar injection or tarsal conjunctival abnormalities.

8 DISCONTINUATION FROM THE STUDY

Participants may be discontinued at the discretion of the investigator or sponsor in consideration of participant safety or protocol compliance, or at discretion of the participant. Participants discontinued from a study will be reimbursed $20 per hour for their active involvement in the study (including the initial screening visit). Upon discontinuing, a participant will be offered the option of their data being withdrawn from future statistical analysis. The following is a list of possible reasons for discontinuation from the study:

- Screening failure: Participants will be discontinued if they do not meet the inclusion and exclusion criteria outlined in section 4.2.3.
- Unacceptable performance with products to be used in study: Participants may be discontinued if they are unable to achieve acceptable comfort and /or vision with the study products.
- Positive slit lamp finding: Participants may be permanently discontinued from the study depending on the severity of the condition and on the judgement of the investigator.
- Adverse event: If a participant experiences an adverse event during the study they may be discontinued based on the clinical judgement of the investigator.
- Symptoms: If the participant has persistent symptoms they may be discontinued based on the clinical judgement of the investigator.
- Disinterest, relocation or illness: The participant may choose to discontinue due to reasons within or beyond their control.
- Violation of protocol or non-compliance: The participant will be discontinued if they are unable or unwilling to follow the protocol specified visit schedules and/or study procedures.
- Instillation of topical ocular medication: The participant will be discontinued if they elect to use a topical ocular medication during the study unless that topical ocular medication is prescribed for a limited duration (less than two weeks) to treat a transient condition; in

this case the participant may remain an active participant (at the discretion of the investigator) after stopping topical ocular medication following resolution of the ocular condition).

- Lost to follow-up: The participant will be discontinued if they cannot be contacted and do not return for a final exit visit, and if the investigator has made a reasonable effort to contact the participant for a final study visit.
- Premature termination of the study by the sponsor, CORE or the Office of Research Ethics at the University of Waterloo.

A discontinuation form, stating the reason for discontinuation will be completed, which requires the signatures of both the participant and the investigator except where the participant is lost to follow-up in which case only the signature of the investigator is required.

All discontinuations including their reasons will be included in the final report.

9 STUDY COMPLETION AND REMUNERATION

At the last scheduled protocol visit a study completion form will be completed, which requires the signatures of both the participant and the investigator.

Once their involvement in the study is complete, participants will be informed about receiving feedback following study completion in the Letter of Appreciation.

Participant remuneration will be $80 for completing the study. In the event that participants withdraw or are discontinued from the study, they will receive $20 per hour for the time that they were involved in the study.

10 STATISTICAL ANALYSIS AND DATA MANAGEMENT

10.1 STATISTICAL ANALYSIS

All data will be analyzed by CORE at the University of Waterloo on unmasked data using Microsoft Excel and statistical analysis software such as GraphPad and SPSS. Interim data analysis will be conducted after 10 symptomatic and 10 asymptomatic participants have completed the study to determine the optimal time period over which to calculate the slope. The results of the interim data analysis will also be used to calculate the sample size.

Descriptive statistics will be provided on information regarding baseline variables (age, sex, contact lens refractive error distribution, etc.). Data may be evaluated for individual groups

(asymptomatic versus symptomatic) and when both groups are combined. Data will be tested for normality of distribution using Shapiro-Wilk tests. A *p*-value of < 0.05 will be considered statistically significant. Additional analysis may be conducted.

Table 4 lists the primary outcome variables and anticipated statistical procedures.

Table 4: Outcome variables and anticipated statistical procedures

Variable	Analysis	Statistical test
Tear evaporat on rate	Change n re at ve hum d ty over t me	S ope
Tear evaporat on rate/T me	Effect of ens type	RMANOVA Mauch y's test of spher c ty Greenhouse-Ge sser *p* va ues Tukey HSD post hocs Pa red t-test
Tear evaporat on rate/ Subject ve rat ngs/Non-nvas ve break up t me/L p d ayer th ckness (L p V ew II - cont nuous)/Area of the ocu ar surface	Re at onsh p between tear evaporat on rate and subject ve comfort and dryness/other tear f m assessments	Pearson corre at on – r
Tear evaporat on rate/ L p d ayer th ckness (Tearscope - ord na)/ Vo ume ns de the gogg e	Re at onsh p between tear evaporat on rate and p d ayer th ckness	Spearman corre at on – rho

10.2 DATA MANAGEMENT

Data from this study will be retained by CORE for a minimum of 25 years on a password-protected server. After 25 years, data will be disposed of in accordance with the guidelines laid out by the University of Waterloo.

10.3 COMMENTS ON SOURCE DOCUMENTS

Data analysis will not be conducted on comments which have been recorded in the source documents. Only relevant and applicable comments will be included in the final report as deemed necessary by the lead investigator.

11 PROTOCOL TRAINING

All study personnel will be required to complete training prior to their involvement in the study. A series of training modules will be developed for the study and records of training will be kept at CORE.

12 STUDY MONITORING

Study monitoring will be conducted by CORE personnel. Consent documentation will be reviewed by a person not involved in the consent process. To improve data integrity, data entry will be double-entered and the entries will be compared for discrepancies. All adverse events and protocol deviations will be reviewed by the Lead Investigator. All serious adverse events and major protocol deviations will be reviewed by the Principal Investigator.

13 STUDY MANAGEMENT

13.1 STATEMENT OF COMPLIANCE

This clinical study is designed to be in compliance with the ethical principles in the Declaration of Helsinki, with the ICH guidelines for Good Clinical Practice (GCP), with the University of Waterloo's Guidelines for Research with Human Participants and with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2nd Edition.

- Declaration of Helsinki
- ICH E6 - International Conference on Harmonisation; Good Clinical Practice
- http://iris.uwaterloo.ca/ethics/human/guidelines/index.htm
- http://iris.uwaterloo.ca/ethics/human/ethicsReview/UWStatement.htm
- http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/

13.2 ETHICS REVIEW

This protocol will be submitted to and reviewed through the Office of Research Ethics (ORE) at the University of Waterloo. Notification of ethics clearance of the application is required prior to the commencement of the study.

13.3 CLINICAL TRIAL REGISTRATION

The study will be registered with clinicaltrials.gov.

13.4 PROTOCOL DEVIATIONS

Protocol deviations are unanticipated or unintentional changes to a study after it has received prior sponsor approval and ethics clearance. Protocol deviations can be major or minor.

13.4.1 MAJOR PROTOCOL DEVIATIONS

Major protocol deviations may impact the research protocol, information consent document or other study materials, usually cannot be anticipated ahead of time and are often necessary to ensure the safety and welfare of the participants.

The following are examples of protocol deviations that must be reported to the ORE:

- Changes in procedures initiated to eliminate immediate risks/hazards to participants;
- Enrollment of participants outside the protocol inclusion/exclusion criteria whether agreed to or not by the sponsor;
- Medication / device / intervention errors (i.e. incorrect drug or dosage of drug / incorrect contact lens(es) dispensed / incorrect care system dispensed);
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention which could impact upon the safety or efficacy of the study-related intervention or upon the experimental design;
- Information consent documentation violations: no documentation of informed consent; incorrect version of, or incomplete, informed consent documentation used.

13.4.2 MINOR PROTOCOL DEVIATIONS

Protocol deviations caused by or which originate with research participants are considered minor, and normally are not reported to the ORE unless these result in increased risk to the participant(s). The following are examples of protocol deviations that are considered minor and do not require reporting to the ORE:

- Logistical or administrative aspects of the study (e.g., study participant missed appointment, change in appointment date);
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention which would not impact upon the safety or efficacy of the study-related intervention or upon the experimental design (i.e., missing a measurement during a session that is not considered critical for the study).

13.4.3 REPORTING AND DOCUMENTING PROTCOL DEVIATIONS

Major protocol deviations must be reported to the ORE within 7 days of the deviation occurring (or its discovery) using the Protocol Deviation Report Form 107 (PDRF). Information from the PDRF is provided to the Clinical Research Ethics Committee (CREC) at the next monthly meeting.

All protocol deviations (major and minor) occurring during the study will be documented and included in the final report.

13.5 PREMATURE TERMINATION OF THE STUDY

CORE or the Office of Research Ethics at the University of Waterloo may terminate the study at any time for any reason.

13.6 STUDY PARTICIPANT RECORDS

Study participant records will be completed to comply with GCP guidelines. Records will contain:

- Unique study acronym and/or code;
- Participant ID;
- Date enrolled;
- Confirmation by investigator that participant met eligibility criteria;
- Confirmation that participant received a signed and dated copy of informed consent;
- Exit date;
- Investigator's signature confirming study exit.

13.7 RETENTION OF STUDY RECORDS AND DATA

Records and data from this study will be retained for a minimum of 25 years. Details regarding storage procedures are given in CORE SOP014_v02 Clinical data management.

14 REPORT

A report will be generated after completion of the study. An internal reviewer will review the report.

15 REFERENCES

1. *The epidemiology of dry eye disease: report of the epidemiology subcommittee of the international dry eye workshop (2007).* Ocul Surf, 2007. **5**(2): p. 93-107.
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3. Nichols, J.J. and L.T. Sinnott, *Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye.* Invest Ophthalmol Vis Sci, 2006. **47**(4): p. 1319-28.
4. Willcox, M.D.P., et al., *TFOS DEWS II tear film report.* Ocul Surf, 2017. **15**(3): p. 366-403.

5. Rohit, A., et al., *Validating a new device for measuring tear evaporation rates.* Ophthalmic Physiol Opt, 2014. **34**(1): p. 53-62.

6. Tsubota, K. and M. Yamada, *Tear evaporation from the ocular surface.* Invest Ophthalmol Vis Sci, 1992. **33**(10): p. 2942-50.

7. Guillon, J.-P. and M. Guillon, *Contact lens practice*, M. Ruben and M. Guillon, Editors. 1994, Chapman & Hall: London, UK ; New York, NY, USA. p. 453-483.