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Centre for Ocular Research & Education

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Protocol

COMPARISON OF TEAR EVAPORATION RATE WITH SYSTANE® COMPLETE IN DRY EYE AND NON-DRY EYE (BULLDOG)

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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

The worldwide prevalence of dry eye is estimated to be approximately 5% to 50%.[1] Dry eye is classified into three main subtypes: aqueous deficient, evaporative, and mixed.[2] In order to effectively treat patients, it is important for eye care practitioners to be able to differentiate between the different causes of dry eye.[3]

One non-invasive method of assessing the rate of evaporation of the tear film from the front surface of the eye is by using a technique called evaporimetry. At present, there is only one commercial evaporimeter, the Eye-VapoMeter (Delfin Technologies Ltd., Finland), available for clinical use. 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.[4]

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, developed by Tsubota and Yamada in 1992, which was capable of binocularly measuring the tear evaporation rate (TER).[5]

The 2017 TFOS DEWS II Tear Film report noted that there is currently a lack of reliable, commercially available evaporimeters and 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.[6] 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.

Due to the relative lack of previously published research investigating evaporimetry and eye drops, the purpose of this pilot study is to compare the effect of an eye drop (Systane® Complete) on TER. Systane® Complete was released in Canada in 2018 for the treatment of both aqueous deficient and evaporative dry eye. The study will also serve to validate the use of the novel, in-house developed evaporimeter for use in non-contact lens wearing participants.

2 OBJECTIVES

The objective of the study is to compare the rate of tear evaporation, measured with a novel evaporimeter, before and for one hour after an eye drop containing nano-sized oil droplets has been instilled.

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

Other variables of interest include:

- Ocular Surface Disease Index (OSDI) score
- Comfort (subjective rating)
- Dryness (subjective rating)
- Burning/stinging (subjective rating)
- Tear meniscus height (mm)
- Non-invasive Keratograph® break up time (NIKBUT)
- Lipid layer thickness (TearScience LipiView® II)
- Ocular surface area (mm^2)
- Volume inside the goggle (cm^3)

3 HYPOTHESIS

The study hypothesis is that instillation of an eye drop will result in lower tear evaporation rates compared to before the eye drop has been inserted.

The second study hypothesis is that dry eye participants will have higher baseline rates of tear evaporation compared to non-dry eye participants.

4 MATERIALS AND METHODS

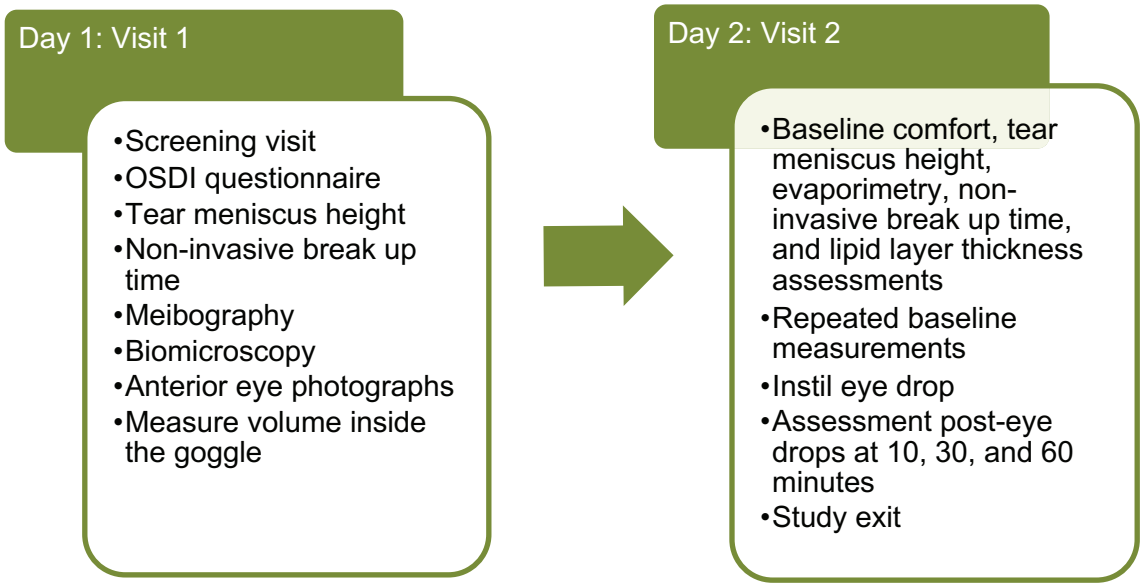
4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

This is a prospective, bilateral, non-dispensing, non-randomized pilot study that will seek to successfully complete 10 dry eye and 10 non-dry eye participants who do not wear contact lenses. More participants are likely will be screened due to the potential for screen failure. The study will involve 2 scheduled visits over 2 days.

Visit 1: Screening visit

Visit 2: Data collection, including instillation of the study eye drop



4.1.2 RANDOMIZATION

There will be no randomization in this study.

4.1.3 MASKING

There will be no masking in this study.

4.2 STUDY POPULATION

4.2.1 SAMPLE SIZE CALCULATION

Because this is a pilot study, a sample size calculation has not been completed. Results from this study will help with sample size determination for future studies.

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

4.2.2 NUMBER OF PARTICIPANTS

Up to 60 participants will be recruited / screened using CORE records and advertising approved by the UW Office of Research Ethics, with a target of 10 dry eye and 10 non-dry eye participants completing the study. At least 20 participants will have the study product instilled at Visit 2. 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 18 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. Is willing to be awake for at least 2 hours before visit 2;
5. Is willing not to wear eye makeup on the day of visit 2;
6. Is willing not to use eye drops or artificial tears on the days of visits 1 or 2;
7. Group specific criteria:
    a. Dry eye participant group: Symptoms: OSDI ≥ 13 and Signs: NIKBUT ≤ 5 s in the worst eye
    b. Non-dry eye participant group: Symptoms: OSDI < 13 and Signs: NIKBUT ≥ 10 s in the worst eye

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 undergone ocular surgery in the last 6 months;
10. Has punctal plugs;
11. Has a known sensitivity to Systane® eye drops (including Systane® Balance, Systane® Complete, Systane® Gel Drops, Systane® Ultra, etc.)
12. Has a known sensitivity to petroleum jelly (Vaseline);
13. Has epilepsy and/or sensitivity to flashing lights;
14. Has worn contact lenses within the past month or is planning to wear contact lenses during the study;
15. Has any physical impairment that would interfere with holding the evaporimeter;
16. Has taken part in another clinical research study involving ocular drops or treatments 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. 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 2 (i.e. 1 repeated screening is allowed).

4.3 STUDY MATERIALS

4.3.1 LENSES

No lenses will be dispensed in this study.

4.3.2 LENS CARE SYSTEM

No lens care system will be used in this study.

4.3.3 LUBRICATING DROPS

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

Table 1: Lubricating drop details

Eye drop	Systane® Complete
Manufacturer	Alcon
HC License #:	100469
Device class:	2
Active ingredients:	Propylene glycol 0.6%
Preservative:	POLYQUAD 0.001%

4.3.4 ORDERING CONSUMABLES

Study products will be obtained through commercial sources.

4.3.5 DISPOSING OF CONSUMABLES

Study products will be disposed of according to UW guidelines.

4.3.6 PRODUCT ACCOUNTABILITY

Accountability logs will be kept to include the number bottles received, used, and unused. All products dispensed to participants will be recorded in the study binder.

4.4 SCHEDULED AND UNSCHEDULED VISITS

This study has a total of 2 study visits, including the screening visit.

- Visit 1: Screening
- Visit 2: Data collection, including instillation of the study eye drop

4.4.1 STUDY VISITS

This study has a total of 2 study visits, including the screening visit. Visit 2 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 for rescreening)	1	Screening	1.5
2	2	2	Data collection & study exit	2.5

4.4.2 VISIT 1: SCREENING

All participants who signed 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 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, current dry eye treatments, medical conditions, medications, allergies)
- Ocular Surface Disease Index (OSDI) questionnaire
- Monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with spectacles (if necessary).
- Tear meniscus height (OCULUS Keratograph® 5M)
- Non-invasive Keratograph® break up time (OCULUS Keratograph® 5M)
- The investigator will confirm that the participant meets the eligibility specifications set out in the inclusion criteria to be categorized as either a dry eye or non-dry eye participant. Participants who do not meet this criteria will be discharged and will not continue with the remainder of the screening visit.
- Lipid layer thickness (EASYTEAR®view+)
- Assessment of meibomian gland secretion and expression
- Lid margin assessment
- Slit lamp biomicroscopy
- Meibography (OCULUS Keratograph® 5M)
- Anterior eye photographs of each eye will be taken with a slit lamp camera.
- Participants will practice evaporimetry measurements.
- 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 (if necessary).
- The investigator will confirm that the participant meets the eligibility specifications set out in the inclusion and exclusion criteria and is eligible to continue with the study.

4.4.3 VISIT 2: DATA COLLECTION

- Participants will attend the visit having been awake for at least 2 hours.
- Participants will not have used any eye drops or artificial tears on the day of the visit.
- Participants will also not have worn any eye makeup on the day of the visit.
- Participants who have used eye drops or artificial tears or have worn eye makeup will be rescheduled.
- Monocular and binocular visual acuity will be recorded with high contrast letters under high illumination with spectacles (if necessary).
- Slit lamp biomicroscopy using white light.
- 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
- Tear meniscus height (OCULUS Keratograph® 5M)
- Baseline evaporimetry measurements
- Non-invasive Keratograph® break up time (OCULUS Keratograph® 5M)
- Lipid layer thickness (TearScience LipiView® II)
- At least 20 minutes after the initial baseline measurement, the participant will be asked to give subjective monocular ratings for:
    - Comfort
    - Dryness
    - Burning or stinging
- Tear meniscus height (OCULUS Keratograph® 5M)
- Repeated baseline evaporimetry measurements
- Non-invasive Keratograph® break up time (OCULUS Keratograph® 5M)
- Lipid layer thickness (TearScience LipiView® II)
- The participant will wipe away petroleum jelly from the skin surrounding the ocular surface using a tissue.

- One drop of Systane® Complete will be instilled into each eye.
- The participant will apply a thin layer of petroleum jelly to the skin surrounding the eye using a cotton tipped applicator to minimise the amount of evaporation from the skin.
- 10 minutes after instillation of the eye drop, the participant will be asked to give subjective monocular ratings for:
    - Comfort
    - Dryness
    - Burning or stinging
- Tear meniscus height (OCULUS Keratograph® 5M)
- Evaporimetry measurements
- Non-invasive Keratograph® break up time (OCULUS Keratograph® 5M)
- Lipid layer thickness (TearScience LipiView® II)
- 30 minutes after instillation of the eye drop, the participant will be asked to give subjective monocular ratings for:
    - Comfort
    - Dryness
    - Burning or stinging
- Tear meniscus height (OCULUS Keratograph® 5M)
- Evaporimetry measurements
- Non-invasive Keratograph® break up time (OCULUS Keratograph® 5M)
- Lipid layer thickness (TearScience LipiView® II)
- 60 minutes after instillation of the eye drop, the participant will be asked to give subjective monocular ratings for:
    - Comfort
    - Dryness
    - Burning or stinging
- Tear meniscus height (OCULUS Keratograph® 5M)
- Evaporimetry measurements
- Non-invasive Keratograph® break up time (OCULUS Keratograph® 5M)
- Lipid layer thickness (TearScience LipiView® II)
- The participant will wipe away the petroleum from surrounding the ocular surface using a tissue.
- Slit lamp biomicroscopy

- Exit monocular and binocular logMAR visual acuity will be recorded with high contrast letters under high illumination with spectacles (if necessary).

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.

4.4.4 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	Instrument/application
Informed consent (screening)	√		Investigator
Demographics	√		Investigator
Medical history	√	√	Investigator
Ocular Surface Disease Index (OSDI)	√		Questionnaire (paper)
VA with spectacles (if necessary)	√	√	Visual acuity chart
Tear meniscus height	√	√	OCULUS Keratograph® 5M
Non-invasive Keratograph® break up time (NIKBUT)	√	√	OCULUS Keratograph® 5M
Lipid layer thickness	√		EASYTEAR®view+
Meibomian gland assessment	√		Meibomian Gland Evaluator (lower lid)

Procedure	Visit 1	Visit 2	Instrument/application
Lid margin assessment	√		Slit lamp
Slit lamp biomicroscopy (with staining)	√	√	Slit lamp
Meibography	√		OCULUS Keratograph® 5M
Anterior eye photography	√		Slit lamp and camera
Evaporimetry practice	√		Prototype evaporimeter
Measurement of volume inside the goggle	√		Modified swimming goggle
Slit lamp biomicroscopy (safety with staining)	√		Slit lamp
Confirmation of inclusion/exclusion criteria	√		Investigator
Slit lamp biomicroscopy (white light)		√	Slit lamp
Subjective assessment (comfort, dryness, burning/stinging)		√	Questionnaire (paper)
Evaporimetry		√	Prototype evaporimeter
Lipid layer thickness		√	TearScience LipiView® II
Application of petroleum jelly		√	Participant
Removal of petroleum jelly		√	Participant
Instillation of eye drop		√	Investigator
Study completion and exit		√	N/A

4.5.1 DEMOGRAPHICS

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

4.5.2 MEDICAL HISTORY

At the screening visit, medical history questions to determine any current medications, current dry eye treatments, 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).

4.5.3 OCULAR SURFACE DISEASE INDEX (OSDI) QUESTIONNAIRE

The OSDI is a dry eye questionnaire that asks the participant to reflect and rate their symptoms of eye dryness in different working conditions and environments over the past week. A higher composite score indicates more severe dryness and scores can range from 0 to 100. A score of <13 will be considered asymptomatic and a score ≥ 13 will be symptomatic.

4.5.4 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 (if necessary).

4.5.5 TEAR MENISCUS HEIGHT (TMH)

The participant will be seated in front of the OCULUS Keratograph® 5M (K5M) with their chin on the chin rest and head against the forehead rest. The investigator will select the Tear Meniscus Height feature from the TF-Scan section on the K5M. The infrared (IR) illumination setting will be used. The camera will be adjusted so the tear meniscus is in the centre of the image. The device will project rings of light (Placido discs) onto the tear film. The participant will be instructed to look straight ahead and an image of each eye will be taken. TMH will be calculated as the average of two measures taken using the on-screen calipers.

4.5.6 OBJECTIVE NON-INVASIVE KERATOGRAPH® BREAK UP TIME (NIKBUT)

The participant will be seated in front of the OCULUS Keratograph® 5M with their chin on the chin rest and head against the forehead rest. The investigator will select the NIKBUT feature from the TF-Scan section on the K5M. The participant will be instructed to blink twice and then keep looking straight ahead while keeping their eyes open for as long as they can. The K5M software will automatically display the time passed from the second blink until the first distortion of the rings. Three measurements will be taken from each eye and the median value will used for each eye.

4.5.7 LIPID LAYER THICKNESS (EASYTEAR®VIEW+)

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).

4.5.8 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 the centre of the lower eyelid just below the lash line and angled down approximately 15 to 45 degrees. 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 quality and quantity of expression. Quality of expression will be graded as follows using a modified scale based on Bron and Snibson[8]: 0: clear fluid, 1: cloudy fluid, 2: cloudy particulate fluid, 3: inspissated, like toothpaste and 4: waxy, inexpressible. The results for each eye will be summed. The number of meibomian glands yielding lipid secretion will be graded as follows for each eye: 0: >75% (almost all), 1: 50 – 75% (more than half), 2: 25 – 50% (less than half), 3: <25% (only a few), and 4: ~0% (close to none).

4.5.9 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.

4.5.10 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

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 increment) while viewing with cobalt blue light and Wratten filter (if available). Conjunctival staining will be graded using a 0 to 4 scale (0.5 steps), with larger values indicating increasing severity.

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).

4.5.11 MEIBOGRAPHY

While seated at the OCULUS Keratograph® 5M, the participant will be asked to place their chin on the chin rest and head against the forehead rest. The lower lid will be everted with the investigator's thumb to expose as much of the palpebral conjunctiva as possible. At least one clear infrared image will be taken of the exposed palpebral surface. The upper lid will be everted with a cotton tipped applicator and at least one clear image will be taken. The amount of missing glandular tissue in each lid will be graded from the images using the following Arita et al. scale: Grade 0 = no MG loss, Grade 1 = area of loss less than 1/3 of the total MG area, Grade 2 = area of loss between 1/3 and 2/3 of the total MG area and Grade 3 = area of loss greater than 2/3 of the total MG area.[10] The grade of the lower lid and upper lid will be summed for each eye (Total Meiboscore).

4.5.12 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.

4.5.13 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 syringe will be used for each participant. New saline and a new pipette tip be used to fill each goggle.

4.5.14 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

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 will be graded using a 0 to 4 scale (0.5 steps), with larger values indicating increasing severity.

4.5.15 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.

4.5.16 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 when wiping near the lid margin to avoid contaminating the tear film.

4.5.17 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 the following time points during Visit 2:

- Before eye drop instillation (prior to the first baseline evaporimetry measurement)
- Before eye drop instillation (at least 20 minutes after the initial baseline evaporimetry measurement)
- 10 minutes after eye drop instillation
- 30 minutes after eye drop instillation
- 60 minutes after eye drop instillation

4.5.18 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 word document 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.

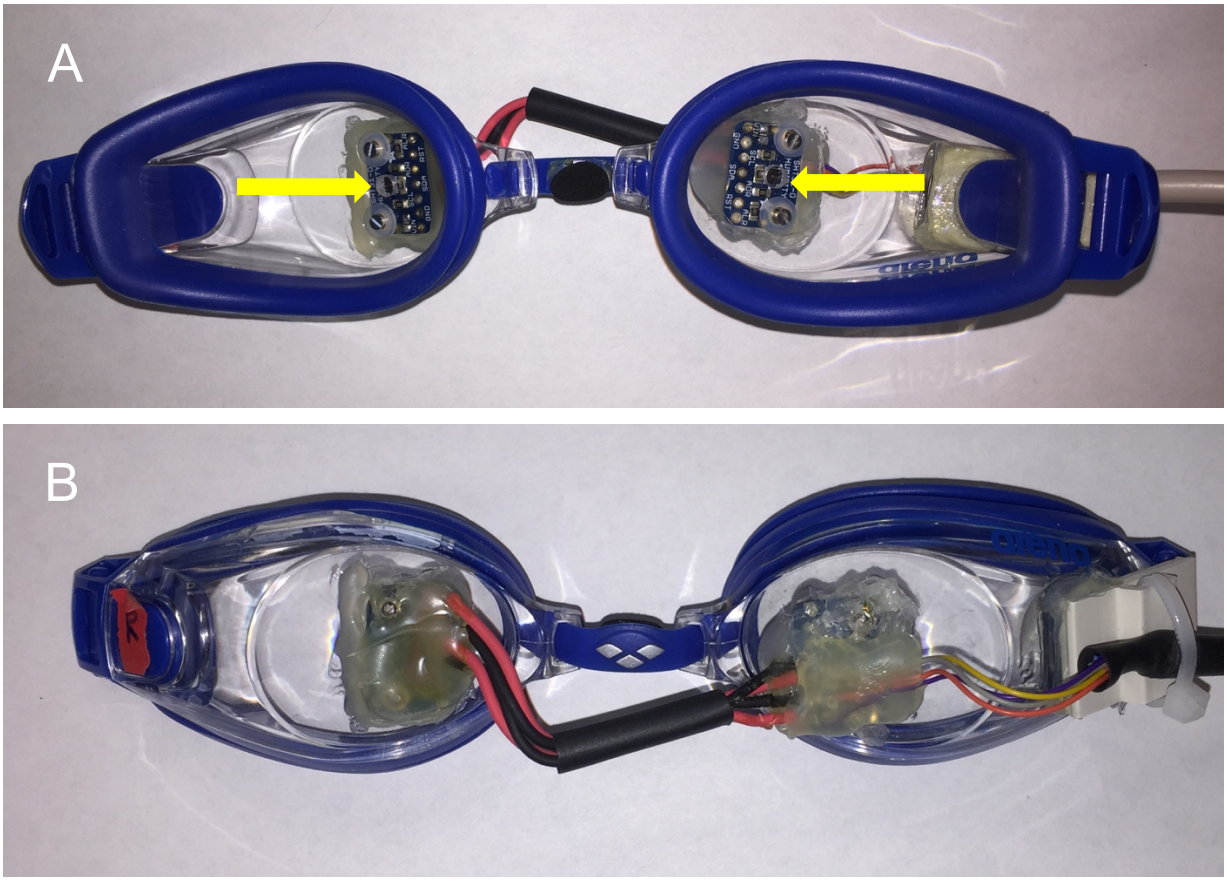


Figure 1: (A) Evaporimeter with arrows showing the location of the temperature/humidity sensors in the swimming goggle. (B) View of the front of the evaporimeter.

4.5.19 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.

4.5.20 INSTILLATION OF EYE DROP

A bottle of SYSTANE® Complete will be well shaken. A couple of drops of SYSTANE® Complete will be transferred to a microtube. The participant will be asked to sit in a consulting chair with their head against the headrest and to tilt their chin up. The participant will be asked to look up and

towards their nose. The lower lid will be lowered and 15 μl of SYSTANE® Complete will be pipetted into the temporal side of the right eye. The participant will be asked to blink their eyes after the eye drop has been instilled. The process will be repeated with a new pipette tip to instil 15 μl of the eye drop into the left eye. A new microtube will be used for each participant.

5 MONITORING PROTOCOL ADHERENCE

Guidelines to be included on adherence to visit windows and windows around other data collection points (i.e. subjective ratings). Procedures for monitoring and reporting deviations from the windows described in the protocol.

6 POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

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

It is possible that participants may experience temporary discomfort associated with the study procedures/devices/eye drops including: eye pain, burning and stinging, blurred vision, sandiness or grittiness, itching, irritation, redness light sensitivity, dryness, itching, crusty eyes, and foreign body sensation.

A dye (fluorescein) normally used to 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 meibography 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 a new device to help others with dry eye in the future. This study may also 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 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. The participants will also be provided with a letter of appreciation.

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.

10 STATISTICAL ANALYSIS AND DATA MANAGEMENT

10.1 STATISTICAL ANALYSIS

All data will be analyzed by CORE at the University of Waterloo using Microsoft Excel and statistical analysis software such as GraphPad and SPSS. Interim data analysis will be conducted after 10 dry eye and 10 non-dry eye participants have completed the study to calculate the final sample size. Descriptive statistics will be provided on information regarding baseline variables (age, sex, etc.). Table 4 lists the primary outcome variables and anticipated statistical procedures.

Table 4: Outcome variables and anticipated statistical procedures

Variable	Analysis	Statistical test
Tear evaporation rate	Change in relative humidity over time	Slope
Tear evaporation rate/Time	Effect of eye drop	RMANOVA Mauchly's test of sphericity Greenhouse-Geisser *p* values Tukey HSD post hocs Paired t-test
Tear evaporation rate/ OSDI/ Subjective ratings/ Tear meniscus height/ Non-invasive Keratograph® break up time/ Lipid layer thickness/ Area of the ocular surface	Relationship between tear evaporation rate and OSDI/ Subjective comfort, dryness, and burning/stinging/ Other tear film assessments/ Area of the ocular surface	Pearson correlation – r
Tear evaporation rate/Volume inside the goggle	Relationship between tear evaporation rate and volume inside the goggle	Spearman correlation - 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 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

CORE will register this study 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);
- 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

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