School of Optometry and Vision Science University of Waterloo 519-888-4567, ext. 33085
200 University Avenue West Fax 519-746-5977
Waterloo, Ontario, Canada optometry@uwaterloo.ca
Faculty of Science, N2L 3G1 www.optometry.uwaterloo.ca

Protocol

Ocular Effects of Scleral Lens Wear on Dry Eye Patients

Protocol authors: [redacted]

Principal Investigator:

Lyndon Jones PhD, DSc, FCOptom

[redacted]

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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

Scleral contact lenses are rigid gas permeable (GP) lenses designed to rest on the sclera while vaulting over the cornea, with a fluid reservoir between the front surface of the cornea and the back surface of the lens. [1] The use of scleral contact lenses has become a standard, non-surgical management method in cases of corneal ectasia and ocular surface diseases.[2-4] Currently, the long-term impact that scleral contact lens wear has on the physiology of the pre-corneal tear film, cornea and limbus especially in dry eye (DE) patients, remains unknow.

Complaints of dryness and discomfort are common in contact lens wearers.[5-9] The use of scleral lenses to restore the integrity of the ocular surface in more severe dry eye has become increasingly accepted among eye care practitioners.[10-12] However, little is known about this treatment regimen and its impact on tear film structure in less severe cases. Therefore, there is a need for a study to determine the effectiveness of scleral contact lens wear in more typically encountered patients with DE complaints.

Understanding factors that influence tear film composition may aid in better understanding of the impact of scleral contact lenses on the health of the cornea. It is also worthy to note that questions regarding the potential impact of coated scleral contact lens designs incorporating Hydra-PEG (polyethylene glycol) technology produced by Tangible Science (Tangible Science LLC, Menlo Park, CA, USA) have not been addressed[13].

This study will provide valuable data on how scleral contact lens material, fit, and surface treatment impact the treatment of dry eye complaints.

2 PURPOSE AND HYPOTHESIS

The purpose of this study is to investigate the effects of scleral contact lens wear on a DE population using coated (Hydra-PEG) and uncoated (control) lenses. Symptoms of DE, quality of the tear film, quality of life, epithelial and overall corneal thickness, vision and comfort will be assessed before and after dispensing and wearing the lenses for four weeks.

The hypothesis is that **coated scleral contact lens wear is associated with improved ocular surface health in patients with dry eye disease (DED)**.

3 OBJECTIVES

The specific objectives are:

1. To evaluate the impact of coated and non-coated scleral contact lenses on DE symptoms.
2. To assess the impact of the lenses on ocular surface health.
3. To measure the comfort and quality of life ratings of each lens type.
4. To determine the subjective ratings of each pair of lenses.

The primary outcome variables are:

1. Epithelial and corneal thickness
2. Quality of the tear film (osmolarity)
3. Levels of protease (inflammatory markers)
4. Contact Lens Impact on Quality of Life (CLIQ) questionnaire score
5. Contact Lens Questionnaire-8 (CLDEQ-8) questionnaire score

Other variables of interest:

- Hours of wear
- Subjective ratings of comfort, dryness, vision and burning.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

This will be a prospective, dispensing cross over study design involving five visits.

The first visit will involve screening, baseline measurements and trial fitting of scleral lenses. At this visit, participants may be wearing their habitual contact lenses (if any) as prescribed by their Optometrist/Ophthalmologist.

The second visit will be a dispensing visit of one of the pairs of the scleral contact lens designs (with or without Hydra-PEG, randomly assigned) and a single follow up visit after 8-10 hours of lens wear in a day, four weeks later (third visit). A washout period of a minimum of 48 hours will be applied between lens types. The fourth and fifth visits will be for the other scleral contact lens visits (delivery and after 4 weeks).

Scleral contact lenses to be worn in this study will be made of Boston XO material (with and without Hydra PEG) approved by Health Canada for commercial purposes. The scleral contact lenses will have a diameter of 14.8-15.4mm. The manufacturer's recommended guidelines will be used to select and fit these lenses, with an expected corneal clearance between 250µm to 350µm. As to which of the two scleral contact lenses are being assessed, both the investigator and the participant will be masked as the Optometric assistant will provide the lenses in an unlabelled case.

Masking the investigator will prevent bias when measuring the primary outcome variables and analyzing the data.

4.2 STUDY POPULATION

4.2.1 SAMPLE SIZE CALCULATION

A minimum sample of 20 DE participants are required to complete the study and thus 25 DE participants will be enrolled. The standard deviation used to determine the sample size was derived from a previous study involving a comparison of fitting scleral contact lenses of different vaults in keratoconus patients and from evaluation of cornea thickness in controls and those having keratoconus (a plausible comparative group).

Power (i.e. the probability of correctly rejecting the null hypothesis) required for this study/experiment is 90% and type-I error is set to 0.05.

4.2.2 NUMBER OF PARTICIPANTS

Recruitment: Participants who are patients of the University of Waterloo (UW) contact lens or ocular health clinics and those who are not UW patients but have previously participated in DE studies through CORE will be invited to participate in this study. With the patient's permission, the investigators will initiate recruitment according to the in-person script or flyers approved by the Office of Research Ethics (Appendices 1a-c). The investigators will discuss the project where any questions regarding the study procedures and any risks associated with the study can be answered. Eligibility will be determined using the inclusion and exclusion criteria. Current contact

lens wear of any lens type is not necessary for the DE participants. Informed consent will be obtained for all participants prior to their enrollment in the study (Appendix 2).

INCLUSION CRITERIA

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

- Is at least 18 years of age and has full legal capacity to volunteer.
- Has read, understood, and signed the information consent letter.
- Has been diagnosed with dry eyes.
- Has reduced tear break up time (NITBUT) and/or reduced tear meniscus height (TMH), clinical sign of dry eye disease and contact lens discomfort or is symptomatic of dry eye.
- Is willing and able to follow instructions and maintain the appointment schedule.
- Has greater than 13 points on the OSDI.
- Has greater than 4 points on the Standardized Patient Evaluation of Eye Dryness (SPEED).

EXCLUSION CRITERIA

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

- Is using any topical medications that will likely affect the study outcome.
- Has undergone any form of corneal surgery.
- Has any known allergies or sensitivity to the diagnostic pharmaceuticals or products, such as fluorescein, used in this study.
- Has persistent, clinically significant corneal or conjunctival staining using sodium fluorescein dye not related to the signs of dry eye.
- Has any clinically significant lid or conjunctival abnormalities and active neovascularization on the cornea.
- Anatomic variations of the conjunctiva that can impair proper scleral or soft contact lens wear/fitting
- Ocular pathology other than dry eye (e.g. glaucoma, macular degeneration) which may significantly impact visual function and assessment.
- Is participating in any other type of eye related clinical or research study.
- Has any active ocular infection and may require topical medications.
- Currently taking any systemic medication that may affect the study outcome.
- Is pregnant
- Has been diagnosed, recovered, or tested positive but asymptomatic with COVID-19.

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. Neovascularisation (non-active) and corneal scars are the result of previous hypoxia, infection or inflammation and are therefore not considered as active ocular disease.

4.3 STUDY MATERIALS

4.3.1 SLIT LAMP BIOMICROSCOPE WITH CAMERA

The slit lamp biomicroscope with mounted high-speed camera, a standard optometric class II medical device, commercially available in Canada (Health Canada licence #69113), will be used to assess the ocular surface and the adnexa during the screening process, contact lens fitting and assessment of the cornea following the contact lens wear.

4.3.2 OCULUS PENTACAM

The Oculus Pentacam HR®, a standard optometric class II medical device which is commercially available in Canada (Health Canada licence #69466) will be used for the measure of corneal curvature and thickness.

4.3.3 KERATOGRAPH 5M

The Oculus Keratograph® 5M, a standard optometric class II medical device which is commercially available in Canada (Health Canada licence #90001) will be used for imaging the corneal surface with fluorescein.

4.3.4 VISANTE OCT

The Visante OCT (Optical Coherence Tomographer), a standard optometric class II medical device, commercially available in Canada (Health Canada licence #69113), will be used to measure the sagittal height of the eye to assist with scleral contact lens fitting.

4.3.5 SPECTRALIS OCT

The Spectralis OCT, a standard optometric class II medical device commercially available in Canada (Health Canada license #76040), will be used to measure the epithelial and corneal thickness before and after scleral contact lens wear. It will also be used to measure the corneal clearance when the lens is initially applied and then after four weeks, for each of the scleral lens designs.

4.3.6 TEARLAB OSMOLARITY SYSTEM

Tearlab Osmolarity System (TearLab Corp. Escondido, CA, USA), a medical device class III which is commercially available in Canada (Health Canada licence #81402) will be used to detect and indirectly measure the levels of osmolarity of the tear film.

4.3.7 INFLAMMADRY® TEST KITS

InflammaDry® (RPS InflammaDry, Sarasota, Florida, USA) is a hand-held, point-of-care diagnostic device (for immunoassay measurements) which is commercially available in Canada and licensed under Labtician Ophthalmics, Inc. (Health Canada licence # 86888). It will be used to detect the levels of protease (MMP-9) in the tear film.

4.3.8 TEAR FILM ANALYSIS

Analysis of the tear film in the scleral lens bowl only will be performed using Meso Scale Discovery system (MSD-ECL). Tears collected at the screening visit (from the ocular surface) will be used as a baseline. After tear collection, the tear samples will be stored at -80ºC until analysis. The tears will be assayed for matrix metalloproteinases and cytokines using commercially available MSD kits. Preparation and analysis of samples will be followed as per instructions supplied by the manufacturer. The tear collection process is detailed in Appendix 19 (SOP for Capillary Tear Film Collection from the Bowl of the Scleral Lens).

4.3.9 SCLERAL CONTACT LENSES

Zen™ RC scleral lenses (non-coated, and Hydra-PEG coated) to be used in this study are approved by Health Canada and are commercially available (license #96602). They are manufactured using the Boston XO material (Health Canada license #71386). All lenses will be worn during the day only. Lenses will be fitted according to manufacturer's recommended guidelines and participants will proceed in the study only if a suitable fit with the lenses can be obtained. This type of conventional lens design will be fitted on both eyes. Appendices 14 and 15 (Package insert for Boston XO and Zen™ RC Fitting Guide respectively).

4.3.10 CONTACT LENS CARE SYSTEM AND ASSESSMENT

The lens care systems that will be used by the investigator/participants during the trial fitting and the dispensing of the scleral contact lens in this study are: Clear Care Disinfecting Solution (Health Canada license #02245661), Boston Simplus Comfort Formula Conditioning solution (Health Canada license #02019868), Sensitive Eyes Saline Plus (Health Canada license #6208410) and Minims Saline (Health Canada license #02148501) (Bausch + Lomb, Rochester, NY, USA). Clear Care and Disinfecting Solution will be used to disinfect the scleral contact lens overnight (minimum of 6 hours) of disinfection. Boston Simplus Comfort Formula Conditioning solution will be used to provide lubrication (initial comfort) on the front surface of the lens before lens application and also to store the lens when not in use. The lenses will be rinsed thoroughly with Sensitive Eyes Saline Plus and filled with Minims Saline before insertion. Sodium fluorescein strips (Health Canada license #02179539) (Fluorets; Laboratoire Chauvin, Aubenas, France) will be used during the trial fitting of the scleral contact lenses.

Participants will be carefully instructed following the manufacturers' recommendation for caring for the lenses before dispensing.

4.3.11 STUDY QUESTIONNAIRES-ANALOG RATING SCALES

The following questionnaires will be used in the study.
As part of the recruitment and the baseline measurements (screening visit), Ocular Surface Disease Index (OSDI) and Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaires will be used to determine the severity and frequency of the DE condition. It will also be used to determine eligibility of the participants (Appendix 4 and 5). Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8) will be used to assess ocular symptoms with the scleral contact lenses at the end of each study visit. (Appendix 8) Contact Lens Impact on Quality of Life (CLIQ) will be used to assess the impact of contact lenses on their daily lives during the wearing schedule. The Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8), Contact Lens Impact on Quality of Life (CLIQ) (Appendix 9) and wearing habit/experience log along with the subjective grading scales (Appendix 10) will be given to the participants to fill out for each week wearing the scleral lenses. The questionnaires will be returned to the investigator during the follow up visits. The standard method of recording the CLIQ questionnaire will be used in the study.

Comfort, vision, dryness, burning and overall preference rating scales (0-100) will be used to assess the subjective responses for each of the contact lenses. These subjective ratings will be done on a weekly basis (at home) and at the end of each study visit.

4.4 SCHEDULED AND UNSCHEDULED VISITS

This study has a total of 5 study visits, including the screening visit (see Table 1).

4.4.1 SCREENING AND TRIAL FITTING

The investigator will determine participant eligibility by reviewing the inclusion and exclusion criteria. The diagnosis of dry eyes will also be confirmed by OSDI and SPEED questionnaires (self-assessed at home and confirmed on first appointment), osmolarity and levels of protease (using inflammadry test kit) in the tear film. Ineligible participants will be advised that they do not meet the criteria for the study. If eligible, then the trial scleral and soft contact lens fittings will be performed following the manufacturer's recommended guidelines.

4.4.2 STUDY VISITS

This study will involve 5 visits over 5 study days in total. The total time commitment for all study visits is approximately 9 hours spread over a 3-month period (See Table 1). The total study visit time commitment may be different for each participant, as the needed visit time will depend on how easily the lenses can be fitted.

The first visit will involve screening and baseline measurements of the participants. The investigator will determine the eligibility of the participant using the inclusion/ exclusion criteria, questionnaires, and tear film analysis (osmolarity and protease levels). Ineligible participants will be discontinued from the study. Eligible participants will be trial fit with the most appropriate scleral lenses (Visit 0-0) as determined by the baseline measurements obtained at the screening visit/appointment. Tear collection from the ocular surface will also be performed as a baseline for comparison with collection from the scleral bowl in the dispensing and follow up visits with the scleral lenses. Participants will be instructed on insertion/application, removal, and proper handling and care of the lenses before dispensing the contact lenses (Visit 1-1, 2-1). Participants will be instructed on insertion, removal, and proper handling and care of the lenses before dispensing the contact lenses (Visit 1-1, 2-1). At each of the lens dispensing/delivery appointments, the researcher will dispense/deliver the study lenses and supplies (contact lens care system). Measurements including visual acuity, topographic corneal clearance, fluorescein assessment will be obtained while the participant is wearing the lenses. The tear collection (from the scleral lens bowl) will be collected immediately the lens is removed from the eye. Study questionnaires (CLDEQ-8, CLIQ and wearing habit/experience log along with the subjective grading scales) will also be handed out to the participants. These questionnaires will be filled each week and biweekly for each of the scleral lens pair for the four weeks wearing schedule.

After the participant has worn the lenses for 8 to10 hours during the day (2 pairs: uncoated scleral contact lens or Hydra-PEG coated scleral contact lens, randomly selected), the participant will return for a follow up visit four weeks later for each pair.
At each of the follow up appointments, evaluation of lens fit, measurements of corneal thickness and assessment of the cornea with slit-lamp biomicroscope will be repeated while the participant is wearing the lenses. Immediately after the scleral lens is removed, the tears will be collected from the bowl of the lens for analysis. Other primary outcome variables (e.g., other questionnaires) will also be collected and reviewed for completeness. (Visit 1-2, 2-2).

A wash-out period of minimum of 48 hours is required between the first lens, follow up visits and the second pair of lenses (scleral lenses). Table 1 Provides a summary of the study visits.

Table 1 Summary of the study visits.

Visit code	Visits	Time
0-0	Screening, baseline measurements and trial lens fitting	2.5hrs
1-1	First lens delivery visit (scleral lenses with or without Hydra-PEG) - Lens 1	2.0hrs
1-2	Follow-up visit (scleral lenses with or without Hydra-PEG)- Lens 1	1.5 hrs
Wash-out Period (48hours minimum)		
2-1	Second lens delivery visit (scleral lenses with or without Hydra-PEG)- Lens 2	1.5hrs
2-2	Follow-up visit (scleral lenses with or without Hydra-PEG)- Lens 2)	1.5 hrs

4.4.7 UNSCHEDULED VISITS

Unscheduled visits will be performed if necessary.

4.5 STUDY PROCEDURES

4.5.1 SCREENING AND BASELINE MEASUREMENTS

Screening & Baseline procedures: Participants will present to the screening visit. The cornea sagittal depth/height will be measured with the Visante OCT. OSDI and SPEED will be collected from the participant. Confirmation and change of dry eye status will be assessed based on tear

osmolarity and MMP-9 measurements using the Tearlab Osmolarity System and InflammaDry® test kits respectively. Additionally, their auto-refraction, visual acuity measurements as well as corneal topography with the Pentacam will be carried out. Eligibility will be confirmed, and a baseline biomicroscopy assessment will be performed to assess corneal. (Visit 0-0).

Ocular Surface Imaging: The eyes of the participants will be examined at the slit-lamp biomicroscope and imaged using the Keratograph® 5M. Participants will be seated at the Keratograph® 5M instrument and asked to blink 2-3 times and hold their eyes open for a few seconds until the instrument software takes a picture of the eye. This image acquisition will be repeated twice. This procedure will also be used to assess corneal and conjunctival staining. (Visits 0-0; 1-1; 2-2).

Fitting of the scleral lenses: Participants will be trial fitted with a scleral lens design using the Pentacam software and following the manufacture's recommendation, but one pair will be ordered non-coated and the other pair will be Hydra-PEG coated (randomly selected). Acceptable fitting will be based on manufacturer's recommended guidelines for fitting these lenses. All scleral lenses used in the study will be made of Boston XO material. Participants will be instructed on insertion, removal, and proper handling of lenses (Visits 0-0, 1-1 2-1).

Imaging procedure With and Without Test Lenses: The anterior segment of the eye and the lens fit will be imaged and assessed using the Visante OCT, Keratograph 5M, Pentacam and Spectralis OCT prior to lens wear and after the lens delivery appointment (Visits 1-1, 2-1), and at the follow up appointment (Visits 1-2, 2-2).

Corneal Thickness Measurements: Corneal thickness will be measured with the Spectralis OCT and Pentacam before and after lens wear (Visits 0-0, 1-2, 2-2). Participants will be seated at the Spectralis OCT and the Pentacam instruments and to blink 2-3 times then hold their eye open for a few seconds until the instrument software takes a measurement of the corneal thickness. This measurement will be repeated twice.

Visual Acuity Assessment: At the screening and follow up appointments (after four weeks of each lens wear), visual acuity will be assessed using the standard LogMAR visual acuity chart. (Visits 1-2 & 2-2).

Contact Lens Dry Eyes, Quality of life assessment and Wearing experience: CLDEQ-8 (biweekly), CLIQ (weekly) and wearing habit/experience along with subjective grading scales (daily) will be used to assess ocular symptoms, quality of life and wearing experience of each of the two pairs of lenses following the four weeks wearing schedule (8-10hrs daily wear). (Visits 1-2, 2-2). These questionnaires will be filled by the participants daily, weekly, and biweekly respectively for each of the pairs of lenses for the four-weeks wearing schedule.

4.5.2 CONTACT LENS DISPENSING/DELIVERY VISIT

Participants will present at the dispensing/delivery visit (visits 1-1, 2-1). The cornea will be assessed with slit lamp biomicroscope. Participant will be asked to insert the contact lenses on the eye. The lens will be examined with the slit lamp biomicroscope with mounted camera. This will be followed by visual acuity and imaging with the Spectralis OCT (to assess corneal clearance and corneal thickness measurements). Before dispensing the contact lens, the investigator will make sure that the participant is confident in inserting/applying, removing and caring for the contact lenses. The appropriate contact lens care system will also be dispensed with the lenses.

The (CLDEQ-8), CLIQ and wearing habit/experience along with subjective grading questionnaires will be administered to the participant to fill out for the four week's wearing period. These questionnaires will be submitted on the next appointment and reviewed for completeness (follow up visit).

4.5.3 FOLLOW-UP VISIT

Following the four weeks of the contact lens wear, the participant will present at the follow-up visit (visits 1-2, 2-2). The lens will be examined with the slit lamp biomicroscope. This will be

followed by visual acuity and imaging with Spectralis OCT (to assess corneal clearance and cornea thickness).

The investigator will carefully remove the contact lens from the eye and immediately collect the tears from the lens bowl for tear analysis. Levels of protease and cytokines in the tears will be assessed.

Slit lamp biomicroscopy mounted camera will be used to assess the corneal integrity and staining. This will be followed by imaging with the Keratograph 5M (for staining) and Spectralis OCT for corneal thickness measurements.

The questionnaire administered (CLDEQ-8, CLIQ and wearing habit/experience along with subjective grading scales) will be collected and reviewed for completeness.

The above-described procedures will be followed for all the lenses to be used in the study.

Table 2 lists a summary of procedures to be conducted at scheduled visits.

Table 2: Summary of procedures at scheduled visits

Visit	Procedure	Instrument/ application	Form (Appendix #)
Screening, Baseline visit and Trial Lens Fitting (Visit 0-0)	Informed Consent	-	ICL (2)
	Demographics & Med. History	-	Screening Form (3)
	Ocular surface disease	Self-Administered Questionnaire	OSDI questionnaire (4)
	Evaluation of Eye Dryness	Self-Administered Questionnaire	SPEED questionnaire (5)
	Vision assessment	LogMAR chart	Study Visit Form for Scleral Lenses (6)
	Osmolarity	Tearlab osmolarity system	Study Visit Form for Scleral Lenses (6)
	Level of protease (MMP-9)	InflammaDry	Study Visit Form for Scleral Lenses (6)
	Tears from ocular surface	Micropipette tear collection kit	Study Visit Form for Scleral Lenses (6)
	Ocular surface imaging	Keratograph 5M (K5M)	Study Visit Form for Scleral Lenses (6)
	Sagittal height/corneal topography	Visante, Spectralis and Pentacam	Study Visit Form for Scleral Lenses (6)
	Biomicroscopy	Slit-lamp with camera	Biomicroscopy Form (7)
	Auto-refraction	Auto-refractor	Study Visit Form for Scleral Lenses (6)
	TRIAL LENS FITTING		
	Lens fitting and examination	Slit lamp with camera	Study Visit Form for Scleral Lenses (6)
	Vision assessment	LogMAR chart	Study Visit Form for Scleral Lenses (6)
	Lens fit evaluation (Clearance)	Visante and Spectralis	Study Visit Form for Scleral Lenses (6)
Lens Delivery (Visits 1-1, 2-1)	Biomicroscopy/VA	Slit-lamp with camera/LogMAR	Biomicroscopy Form (7) and 6
	LENS INSERTION, ASSESSMENT, DISPENSING AND QUESTIONNAIRE		
	Lens examination	Slit lamp with camera	Study Visit Form for Scleral Lenses (6)
	Vision assessment	LogMAR chart	Study Visit Form for Scleral Lenses (6)
	Lens fit evaluation (clearance, etc)	Visante, Spectralis	Study Visit Form for Scleral Lenses (6)
	Tear Collection	Taken from Bowl of Scleral Lenses	Study Visit Form for Scleral Lenses (6)

	Ocular symptom questionnaire (2x)	Self-Administered Questionnaire	Ocular Symptom Questionnaire (8)
	Quality of life questionnaire (4x)	Self-Administered Questionnaire	CLIQ questionnaire (9)
	Subjective ratings	Analogue Scales	Wearing Habit Log Form (10)
Follow-up visit (Visits 1-2, 2-2)	Vision assessment	LogMAR chart	Study Visit Form for Scleral Lenses (6)
	Lens examination	Slit lamp with camera and K5M	Study Visit Form for Scleral Lenses (6)
	Lens Fit Evaluation (clearance)	Visante and Spectralis	Study Visit Form for Scleral Lenses (6)
	CONTACT LENS REMOVAL, ASSESSMENT, QUESTIONNAIRE REVIEW		
	Tear Collection	Taken from Bowl of Scleral Lenses	Study Visit Form for Scleral Lenses (6)
	Biomicroscopy	Slit-lamp with Camera and K5M	Biomicroscopy Form (4)
	Sagittal height/topography	Pentacam and Spectralis OCT	Study Visit Form for Scleral Lenses (6)
	Osmolarity	Tearlab osmolarity system	Study Visit Form for Scleral Lenses (6)
	MMP-9	InflammaDry	Study Visit Form for Scleral Lenses (6)
	Questionnaire Review	CLDEQ-8, CLIQ, Wearing log	Appendices 6,8 and 9
	Participant exists study	-	Remuneration form

5 POTENTIAL RISKS AND BENEFITS TO HUMAN SUBJECTS

Participants may or may not derive a direct benefit of the study. Participants will benefit from having had the opportunity to try scleral lenses (non-coated and Hydra-PEG coated), which is one of the newest lenses designs in the market for vision correction. If there is a benefit that the participants report, then they will be permitted to keep a pair of scleral lenses, so far as they continue to seek care from UW-CLC or their own contact lens specialist.

This study gives insight to eye care providers on whether non-surface coated, or surface coated scleral contact lens have the capacity to improve the ocular physiology, reduce dryness, and improve the quality of life in patients with dry eyes. This study may benefit optometric practitioners and clinical scientists on a potential new option to reconsider non-pharmacological agents such as contact lenses as one of the possible options for treating/managing dry eye conditions. This knowledge will help practitioners make informed decision for their dry eye patients based on clinical ocular surface characteristics/findings of their patients vis-à-vis lens design, material, surface treatment/modification, wearing schedule and the technology involved in producing these lenses. This is so because different lenses have different interactions with the front surface of the eye and with the improved designs and chemistry, contact lenses may lead to a new path in the management for dry eyes. Participation in this study may also contribute to scientific research information that may be used in the development of new contact lenses based on the chemistry of the material, surface treatment options and interaction with pre-corneal tear film. This may help provide improved comfort and reduce contact lens wear dropouts. The optometric community will benefit as they will have a better understanding of how selection of either non-coated or coated scleral contact lenses could make a significant impact in regaining and maintaining the integrity of the ocular physiology, thereby improving comfort for dry eye patients.

This study is considered a non-significant risk study based on United States Food and Drug administration (FDA) and International Standards Organization (ISO) guidelines due to the daily wear of the lenses in the study.

The scleral lenses to be used in this study are approved by Health Canada and are commercially available. The lenses are intended for daily wear (NOT extended wear). Because this study is a dispensing study, participants' lens wear will be monitored closely by the investigators. Participants can contact the investigator by phone and email at any time throughout the study.

Complications that may occur during the wearing of contact lenses include discomfort, dryness, aching or itching eyes, excessive tearing, discharge, hyperemia (redness) and variable or blurred vision. More serious risks may include photophobia, iritis, corneal edema or eye infection. Although contact lens-related infections are very infrequent with GP contact lenses, the possibility does exist. The occurrence rate of incurring a bacterial infection for patients that wear GP contact lenses is approximately 2/10,000 per year. (5)
If the participant should experience any pain or discomfort during lens wear, any of the symptoms described above, or there is any health concern or a case of emergency, they are instructed to contact CORE at 519 888-4742 or [redacted] ((519) 888-4567 extension 36210, using the information on the wallet card. (Appendix 18)

Although participants with any known allergies or sensitivity to the diagnostic pharmaceuticals products or drops such as fluorescein, used in this study would have been excluded, if any irritation occurs, the participant will be instructed to contact the investigators.

Instruments to be used in this study are ophthalmic instruments used frequently in a clinical environment and thus pose no risks to the participant. The Spectralis OCT has been classified as a NSR (non-significant risk) device based on United States Food and Drug Administration (FDA) guidelines. In OCT imaging, all exposures to light from the semiconductor optical amplifier (SOA) source are kept within documented safe limits. The light from the SOA source that will be used for optical ranging will be at the infrared. The limits for safe ocular exposure to laser light have been well established and are documented by the American National Standards Institute, ANSI Z136.1-1993. The ANSI standard for maximum permissible exposure (MPE) for 1300 nm light is 4.9 mW assuming full pupil intrabeam viewing (7 mm pupil aperture) for long exposure times (up to 103 seconds) with the light being focused on the retina. The real time OCT system will comply with this standard, which is especially conservative in our case, since in anterior segment OCT, light is focused on the cornea, so that the light reaching the retina is out of focus. The output light can be set up to 1.4 mW and the actual measured output is 1.14 mW, which is well below ANSI Z136.1-2000 standards for safety. Therefore, the measurement is non-invasive and safe.

Parts or all of this study will be conducted during the COVID-19 pandemic. Therefore, risks of infection with COVID-19 exist through participation. These risks arise due to possible exposure during commute to and from the study visit as well as during the study visit, particularly due to the closeness of the investigator and participant (within 2m for some assessments). The potential effects of COVID-19 are not yet fully known and may include long-term health consequences. In a small percentage, infection with COVID-19 can lead to serious illness, hospitalization, and in rare cases to complications leading to death. Individuals aged 60 and above and those with underlying medical conditions are considered at a greater risk for severe illness from the COVID-19 virus.

In consideration of risks associated with COVID-19, CORE has implemented a series of on-site safety procedures which have been reviewed and approved by the University of Waterloo. These include, but are not limited to, self-screening of investigators and participants prior to entering the building, maintaining physical distancing as much as possible, frequent handwashing, wearing of face masks by the investigator and participant, and frequent room and equipment hygiene and decontamination.

6 UNINTENDED EVENTS

The imaging procedures outlined in this protocol will be carried out with instruments that are typically used in any optometric practice and therefore, there are no anticipated or unintended events.

7 DISCONTINUATION FROM THE STUDY

Participants discontinued from a study will be compensated for each attended visit ($20/hr) in the study. Participants will be discontinued at the discretion of the investigators or participant. 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 4.2.2
- 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.
- Unexpected adverse event: If a participant experiences an adverse event (excessive redness or dryness), at the discretion of the investigator, the participant may be excluded from the study.
- Symptoms: If the participant has persistent symptoms (excessive redness or dryness ascertained by any of the questionnaires or at any visit), the participant may be discontinued from the study 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.
- Lost to follow-up: The participant will be discontinued if they cannot be contacted and does 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 Office of Research Ethics at the University of Waterloo.

8 STUDY COMPLETION AND REMUNERATION

Once their involvement in the study is complete, participants will be informed about receiving feedback following study completion in the Letter of Appreciation (Appendix 11).

Participant remuneration will be $180 for completing the study and is typically paid at the end of the study (Appendix 12). This remuneration can be in a form of cheque or Amazon gift card and participants will be asked to choose one of the two options. One pair of the study lenses may kept by participants at the end of the study as long as they continue care with UW-CLC or their own contact lens specialist.

9 STATISTICAL ANALYSIS AND DATA MANAGEMENT

9.1 STATISTICAL ANALYSIS

All data described above will be analysed at the University of Waterloo from the eyes wearing the scleral lenses. Data analysis will be conducted using Statistica 13. Descriptive statistics will be used to analyse the baseline variables (age, gender, sagittal depth distribution, etc.). Table 3 lists the primary outcome variables and anticipated statistical procedures.

Table 3: Statistical procedures

Variable	Analysis	Statistical test
Parametric: tear clearance, corneal thickness, epithelial thickness, curvature, vision, osmolarity, comfort ratings	Comparison of lenses 1, 2 Comparison of epithelial and corneal thickness evaluation, osmolarity measurements	Paired t-test ANOVA RM-ANOVA
Nonparametric: OSDI, SPEED, CLDEQ-8, levels of protease	Comparison of ocular symptoms, quality of life, dryness, subjective assessment	T-test Mann-Whitney U test

9.2 DATA MANAGEMENT

At the completion of the study, a report will be generated. Data from this study will be referred to only using study number and will be retained by the PI's for a minimum of 25 years on a password-protected server held by the School of Optometry and Vision Science. After 25 years, data will be disposed of in accordance with the guidelines laid out by the University of Waterloo.

10 PROTOCOL TRAINING

Training of the graduate student will be conducted for this study to educate him about the testing procedures.

11 STUDY MONITORING

Study records may be inspected by the investigator's supervisor, the Office of Research Ethics at the University of Waterloo, and by regulatory authorities in Canada (Health Canada); however, no records containing identifiable/personal information will be permitted to leave the School of Optometry and Vision Science, Contact Lens Clinic.

12 STUDY MANAGEMENT

12.1 STATEMENT OF COMPLIANCE

This clinical study is designed to follow 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
- https://uwaterloo.ca/research/office-research-ethics/research-human-participants
- https://uwaterloo.ca/research/sites/ca.research/files/uploads/files/uw_statement_on_human_research_access_checked.pdf
- http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/

12.2 ETHICS REVIEW

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

12.3 ADVERSE EVENTS

12.3.1 ADVERSE EVENT DEFINITIONS

An 'adverse event' refers to any undesirable clinical occurrence in a participant, whether it is device-related or not. Adverse events (AE) may be classified as 'unanticipated adverse device effects,' 'serious adverse events,' 'significant adverse events,' or 'non-significant adverse events,' as defined below.

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

AE classification, coding and examples are provided in the following table used for reporting.

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

17	Any sign and/or symptom for which participant is administered therapeutic treatment or which necessitates discontinuation of lens wear for ≥ 2 weeks	
10	Other significant event	
Non-significant Adverse Events		
21	Conjunctivitis (bacterial, viral or allergic)	Notify ORE as soon as possible, **within 24 hours**;
22	Papillary conjunctivitis if ≥ mild scattered papillae/follicles approximately 1mm in diameter (e.g. ISO 11890 Grade 2), if 2 grade change from baseline	
23	Asymptomatic corneal infiltrative events	
24	Any sign and/or symptom for which temporary lens discontinuation for > 1 day is recommended (if not already classified)	
20	Other sign and/or symptom warranting classification as a non-significant adverse event	

12.3.1.1 NORMAL OR ADAPTIVE SYMPTOMS

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

12.3.2 PROCEDURES FOR ADVERSE EVENTS

Treatment of an adverse event will depend on its nature and severity. Based on the clinical judgment of the investigator, the participant may be referred to an ophthalmologist for treatment. The investigator will attempt to determine whether the reaction is related to the test device or a result of other factors. An Adverse Event Form (Appendix 13) will be completed for each adverse event. If both eyes are involved, a separate Adverse Event Form will be completed *for each eye*. Whenever possible, the adverse event will be photo-documented.

Expenses incurred for medical treatment as part of study participation will be paid by the School of Optometry and Vision Science (Prof. Lyndon Jones) as the investigator is supported by an independent unrestricted research grant from Bausch and Lomb (bills and prescription receipts kept). The participant must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.

12.3.2.1 REPORTING ADVERSE EVENTS

All potential Serious and Unanticipated Adverse Device Effects that are related or possibly related to participant participation will be reported to the Principal Investigator's supervisor within 24 hours of the investigator becoming aware of the event. The Principal Investigator will report the event to the ORE as soon as possible (by fax, mail/delivery, phone, or email) following the University of Waterloo Office of Research Ethics reporting guidelines. All fatal or life-threatening events will be reported immediately to the ORE.
Significant and Non-Significant Adverse Events will be reported to the ORE within 24 hours.

12.4 PROTOCOL DEVIATIONS

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

12.4.1 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 ethics committee;
- 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.

12.4.2 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).

12.4.3 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.

12.5 PREMATURE TERMINATION OF THE STUDY

The PI's or the Office of Research Ethics at the University of Waterloo may terminate the study at any time for any reason except for premature termination if undesirable results are found.

13 QUALITY ASSURANCE

13.1 STUDY PARTICIPANT RECORDS

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

- Study number;
- Participant ID;
- Date enrolled;
- Confirmation by lead investigator that participant meets eligibility criteria;
- Confirmation that participant received a signed and dated copy of informed consent;

13.2 RETENTION OF STUDY RECORDS AND DATA

Records and data from this study will be retained for a minimum of 25 years. Paper copies of study data will be safely held in a secure storage cabinet in a locked office (Room 248) at the School of Optometry and Vision Science, University of Waterloo and will be only available to personnel involved in the data collection of this study. The electronic research data will be encrypted as per Guidelines laid out by UW Information and Systems Technology and be stored on a password protected server held in a locked office at the School of Optometry and Vision Science. The images we acquire, with all identifying information removed, will be kept on a

secure password protected server stored in a locked office at the School of Optometry and Vision Science. Image data will be saved using a coded file name associated with each participant, and the list of the participants' names and corresponding numbers will be stored in a separate file at UW. Access to electronic data, images, photographs and videos is limited to authorized study personnel.
Records will be confidentially disposed of in accordance with the guidelines laid out by the University of Waterloo. More information regarding the University of Waterloo's policies on information security is available on the following website: https://uwaterloo.ca/secretariat-general-counsel/policies-procedures-guidelines/policy-8.

14 CLINICAL TRIAL REGISTRATION

This clinical trial has been registered with the clinical trials registry at www.ClinicalTrials.gov, under University of Waterloo Protocol Record XXXXXX.

15 REPORT

A report will be generated within 8 weeks after the completion of the study for inclusion in the student investigator's thesis.

16 APPENDICES

Appendix 1a In person script
Appendix 1b Advertisement for DE
Appendix 1c Email recruitment script_Scleral Lenses
Appendix 2 Information consent letter
Appendix 3 Screening form
Appendix 4 Ocular Surface Disease Questionnaire (OSDI)
Appendix 5 Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire
Appendix 6 Study Visit Form for Scleral Lenses
Appendix 7 Biomicroscopy form
Appendix 8 Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8)
Appendix 9 Quality of life Questionnaire (CLIQ)
Appendix 10 Wearing habit/experience log along with analogue grading scales
Appendix 11 Feedback and appreciation letter
Appendix 12 Study Completion/Remuneration Form
Appendix 13 Adverse Event Form (ORE)
Appendix 14 Package Insert Boston XO Material
Appendix 15 Zen™ RC Fitting Guide
Appendix 16 Tearlab User Manual
Appendix 17 InflammaDry Manual
Appendix 18 Emergency Wallet Card
Appendix 19 SOP-Capillary tear film from scleral lens collection

17 REFERENCES

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