PROTOCOL

A comparison of the effects of Alcon DAILIES TOTAL1 and a control high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye, on the biology of the ocular surface and lid margin

Principal Investigator: Danielle M. Robertson, O.D., Ph.D.
Co-Investigator: W. Matthew Petroll, Ph.D.
Biostatistical Collaborator: Chul Ahn, Ph.D.
Department of Ophthalmology
The University of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-9057

Dated: June 15, 2017
Version 9.0
NCT02347631

Table of Contents

1.0 PROTOCOL SYNOPSIS 4
1.1 Background and Significance 4
1.2 Test Hypotheses 4
1.3 Protocol Overview 6
2.0 SPECIFIC OBJECTIVES 7
3.0 STUDY DESIGN 7
3.1 Overview 7
3.2 Study Workflow 8
3.3 Study Population 10
3.3.1 Inclusion/Exclusion Criteria 10
3.3.2 Recruitment 11
3.4 Bias Control Measures 12
3.4.1 Overview 12
3.4.2 Randomization 12
3.4.3 Masking 12
3.4.4 Sample Size Determination and Statistical Methods 12
4.0 PROCEDURES 13
4.1 Pre-randomization Testing 13
4.1.1 Eligibility Determination 13
4.1.2 Baseline Visit 15
4.1.3 Contact Lens Order and Adaptation 16
4.2 Randomization 17
4.3 Post-randomization 17
4.3.1 Scheduling 17
4.3.2 Clinical Assessments 18
4.3.3 Laboratory Assessments 19
5.0 Human Subject Protection 20
5.1 Overview 20

5.2 Informed Consent 20
5.3 Study Personnel 21
5.4 Confidentiality 21
5.5 Criteria for Discontinuing Contact Lens Wear 22
5.6 Safety Monitoring: Adverse Events 23
5.6.1 Serious Adverse Events 23
5.6.2 Adverse Device Effects (A.D.E.) 23
5.6.3 Undesirable Side Effects (U.S.E.) 23
6.0 Data Management, Quality Assurance, and Analysis 23
6.1 Form Management 23
6.2 Data Entry and Storage 24
6.3 Data Quality Assurance 24
6.4 Data Analysis Procedures 24
Appendix 27
A.1 Measurement Procedures 27
A.1.1 Contact Lens Diary 27
A.1. 2 Tear Collection 27
A.1.3 Lid Wiper Staining 27
A.1.4 *In Vivo* Confocal Microscopy 28
A.1.6 Exfoliated Cell Collection and Quantitation 28
A.2 FDA Slit Lamp Findings Classification Scales 30
A.2.1 Edema 30
A.2.2 Corneal Neovascularization 31
A.2.3 Corneal Staining 32
A.2.4 Injection 33
A.2.5 Tarsal Abnormalities 34
A.2.6 Other 35
A.3 Patient Instructions 36

1.0 PROTOCOL SYNOPSIS

1.1 Background and Significance

The new water gradient DAILIES TOTAL1 daily disposable contact lens has been touted as a "revolution" in the evolution of contact lens design with the promise of enhancing comfort, a consistent barrier to the global growth of the contact lens market. With the silicone core and six micron thick hydrophilic surface gel, this lens is designed to mimic the ocular surface and increase lubricity while maintaining optimal oxygen permeability. While all types of contact lens wear have been shown to alter the normal homeostasis of the corneal epithelium resulting in a decrease in apoptotic-mediated surface cell shedding and a corresponding increase in size of surface cells, the cellular impact of the water gradient DAILIES TOTAL1 has not yet been established. The goal of this study is to evaluate the effects of the DAILIES TOTAL1 on the biology of corneal epithelium over two months of daily wear compared to wear of a high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye; and to correlate these changes with alterations in the lid wiper, tear film and cellular changes at the limbus.

1.2 Test Hypotheses

This proposal will test the primary hypothesis that:

A. The magnitude of the reduction in corneal epithelial surface cell exfoliation following wear of the new DAILIES TOTAL1 water gradient lens will be less than the magnitude of the reduction measured following wear of a control, high oxygen permeable silicone hydrogel daily disposable contact lens.

This proposal will test the secondary hypothesis that:

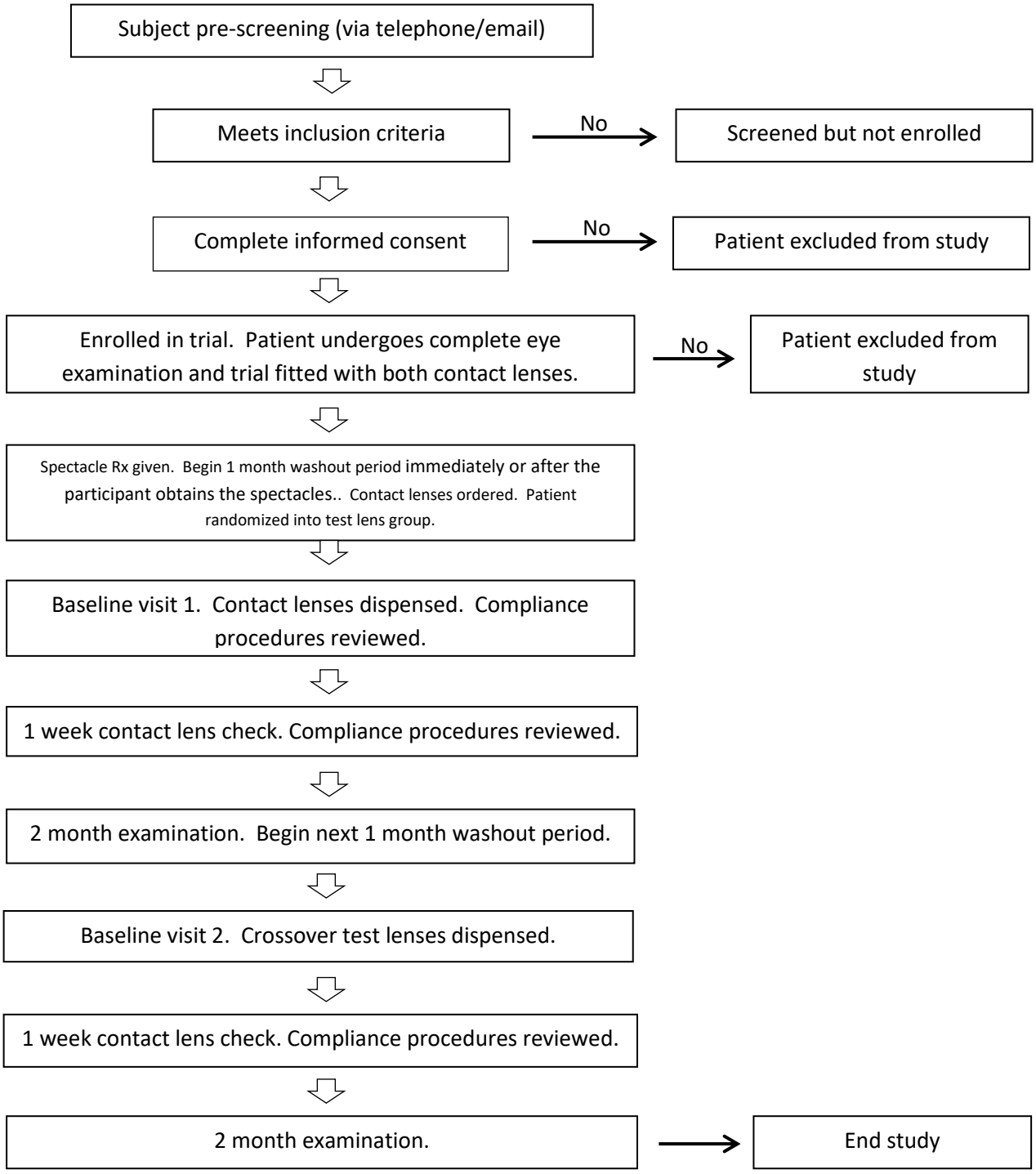
A. The area of corneal surface epithelial cells will not be increased over baseline following wear of the new DAILIES TOTAL1 water gradient lens while the area of corneal surface epithelial cells will be increased following wear of a control, high oxygen permeable silicone hydrogel daily disposable contact lens.

This proposal will test the following exploratory hypotheses:

A. There will be an improvement in the biology of the lid wiper region following wear of the new DAILIES TOTAL1 water gradient lens when compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens.
B. Surface area of limbal epithelial cells will be unchanged following wear of the new DAILIES TOTAL1 water gradient lens, whereas area will be increased following wear of a control, high oxygen permeable silicone hydrogel daily disposable contact lens.

C. Limbal and central epithelial thickness will be unchanged following wear of the new DAILIES TOTAL1 water gradient lens, whereas thickness will be reduced following wear of a control, high oxygen permeable silicone hydrogel daily disposable contact lens.
D. Dendritic cell infiltration in the limbal region will be unchanged following wear of the new DAILIES TOTAL1 water gradient lens, whereas dendritic cell infiltration will be increased following wear of a control, high oxygen permeable silicone hydrogel daily disposable contact lens.
E. Extracellular DNA content of tear fluid will be unchanged following wear of the new DAILIES TOTAL1 water gradient lens, whereas DNA content will be increased following wear of a control, high oxygen permeable silicone hydrogel daily disposable contact lens.

1.3 Protocol Overview



2.0 SPECIFIC OBJECTIVES

1. The primary experimental objective of this study is to characterize the effect of the DAILIES TOTAL1 compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye, on corneal epithelial cell desquamation. This effect will be assessed using a standardized ocular irrigation technique to measure:
    a. Rate of desquamation of corneal epithelial cells (cells/min).

2. The secondary experimental objective of this study is to evaluate the effect of wear of the DAILIES TOTAL1 on the central corneal epithelium compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye. This effect will be assessed using IVCM to measure:
    a. Area of surface epithelial cells within the central cornea (μm^2).

3. Multiple exploratory aims will also be investigated. These aims will be used to evaluate the effects of lens wear on the biology of the corneal and limbal epithelium, lid wiper and changes in the extracellular tear content of DNA in response to wear of the DAILIES TOTAL1 compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye.
   These will be assessed by:
    a. Area of surface epithelial cells within the limbal region.
    b. Dendritic cell infiltration in the limbal region.
    c. Staining of the lid wiper region with sodium fluorescein and lissamine green.
    d. IVCM evaluation of the eyelid.
    e. Quantification of extracellular DNA adherent to the posterior lens surface and in the post lens tear film.

Detailed descriptions of the study design, procedures, data management and human protection are provided in the following sections.

3.0 STUDY DESIGN

3.1 Overview

This is a prospective, single center, randomized, bilateral crossover, dispensing clinical trial to evaluate the effects of the water gradient lens, DAILIES TOTAL1, on the biology of corneal epithelium over two months of daily wear compared to wear of a control high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye; and to correlate these changes with alterations in the lid wiper, tear film and cellular changes at the limbus. The total proposed duration of this study is 12 months to ensure enrollment of up to 140 established contact lens wearers, with anticipated completion of 84. Data will be collected at

baseline and following 2 months of daily wear for each lens type. Based upon data from our previous contact lens clinical trials, a 1 month washout period is required prior to initiating lens wear to eliminate any potential residual solution or lens effects on the corneal epithelium and restore homeostasis. The study is scheduled to commence upon IRB approval.

3.2 Study Workflow

Visit 1: Comprehensive ocular examination (Contact Lens Clinic at UTSW)

a. Informed consent reviewed and signed
b. Comprehensive examination
c. Back-up glasses ordered as needed
d. Lens fitting and ordering based on randomization into the following lens groups:
    i. Alcon DAILIES TOTAL1
    ii. Johnson and Johnson ACUVUE TruEye
e. One month washout begins immediately or after the participant obtains the spectacles.

Visit 2: Baseline Visit, lens 1 dispensed (+/- 3 days)

a. Brief screening exam
b. Informed consent re-reviewed
c. Baseline biological indicators (outcome measures) assessed
    i. Tear collection OU
    ii. Lid wiper staining OD
    iii. Ocular irrigation OS
    iv. Confocal microscopy of cornea, limbus and lid margin OD
d. Lenses dispensed

Visit 3: 1 week of lens wear (+/- 3 days)

a. Contact lens check up
    1. Snellen Visual Acuity Testing
    2. Lens fitting
    3. Slit lamp examination without corneal staining

Visit 4: 2 month of lens wear (+/- 3 days)

a. Brief screening exam
b. Lenses and diaries collected
c. Biological indicators assessed
    i. Lenses collected OU
    ii. Tear collection OU
    iii. Lid wiper staining OD
    iv. Ocular irrigation OS
    v. Confocal microscopy of cornea, limbus and lid margin OD
d. Patient begins next 1 month washout period

Visit 5: Baseline visit, lens 2 dispensed (+/- 3 days)

a. Brief screening exam
b. Baseline biological indicators assessed
    i. Lenses collected OU
    ii. Tear collection OU
    iii. Lid wiper staining OD
    iv. Ocular irrigation OS
    v. Confocal microscopy of cornea, limbus and lid margin OD
c. Lenses dispensed – begin crossover phase

Visit 6: 1 week of lens wear (+/- 3 days)

a. Contact lens check up
    i. Snellen Visual Acuity Testing
    ii. Lens fitting
    iii. Slit lamp examination without corneal staining

Visit 7: 2 month of lens wear (+/- 3 days)

a. Brief screening exam
b. Lenses and diaries collected
c. Biological indicators assessed
    i. Lenses collected OU
    ii. Tear collection OU
    iii. Lid wiper staining OD
    iv. Ocular irrigation OS
    v. Confocal microscopy of cornea, limbus and lid margin OD
d. Study completed

Table 1: Overall study design

Visit No.	Interval	Time in lens	Procedures
1	0	0	Sign and review IC. Comprehensive ocular examination. Order back-up glasses if needed. Lens fitting and ordering. One month washout period of no lens wear.
2	1 month	0	Brief screening exam. Informed consent re-review. Baseline biological indicators assessed. Dispense contact lenses.
3	1 month, 1 week	1week	Contact lens check.
4	3 months	2 months	Lenses and diaries collected. Biological indicators assessed. Begin next washout period.
5	4 months	0	Baseline biological indicators assessed. Lenses dispensed.

6	4 months, 1 week	1 week	Contact lens check.
7	6 months	2 months	Lenses and diaries collected. Biological indicators assessed. Study completed.

3.3 Study Population

The study population will consist of 140 healthy adults aged 18-38 years of age.

3.3.1 Inclusion/Exclusion Criteria

For inclusion in this study, subjects must be:

- Aged 18-38 years
- Any sex, race or national origin accepted as with our past studies. Minority representation will be proactively encouraged
- Sign written informed consent
- A habitual contact lens wearer and only wear lenses for daily wear use (no overnight wear) or non-contact lens wearers wanting to try contact lenses
- Myopia range: -1.00 to -6.00 with regular astigmatism (≤1.00D, both eyes)
- Be willing to wear spectacles for two 1-month washout periods
- Have acceptable fit with test lenses and be willing to wear lenses for the duration of the study.
- Need correction in both eyes and be correctable to within 3 letters (high contrast Snellen VA) of their current contact lens prescription at baseline in each eye with the test lenses.
- No history of allergic eye disease either seasonal or associated with previous contact lens wear.
- A routine screening complete ocular examination (COE) with ocular findings considered to be within normal limits.
- Be willing and able to follow instructions regarding the wear of the daily disposable lenses and attend the scheduled follow-up visits.
- Must be able to arrange weekday appointments between 8:00 AM and 12:00 PM.

Exclusion criteria include:

- Habitual lens wearers unable to wear lenses for a minimum of 8 hours per day.
- Use of concurrent ocular medication
- Habitual toric or bifocal contact lens wearers
- Any previous history of keratorefractive surgery or recent ocular injuries or ocular surgery within the prior 3 months
- Any preexisting ocular disease
- Monocular contact lens wear
- Any systemic disease or ocular abnormality that may impact optimal contact lens wear

- Use of systemic medications including but not limited to antihistamines, corticosteroids, anticholinergics or immunomodulatory agents
- Pregnancy or lactation
- Concurrent enrollment in another clinical trial

3.3.2 Recruitment

3.3.2.a Overview

The clinical contact lens service within the Ophthalmology Department at the University of Texas Southwestern Medical Center employs five full-time optometrists who oversee a high volume contact lens practice with approximately 3,000 patients yearly. There are also seven full-time corneal specialty M.D. faculty and three additional general ophthalmologists who see established contact lens patients. Likewise, the department retains 4 full-time, salaried clinical coordinators who oversee all department clinical trials.

3.3.2.b Recruitment procedures

The following procedures will be utilized on an ongoing basis to ensure timely recruitment.

- The clinical records of ongoing and new patients of the Contact Lens Service and MD faculty will be screened and suitable candidates contacted.
- An advertisement will be placed in the institutional newspaper, "Center Times," which reaches all medical and graduate students, employees, faculty and their dependents, including the major teaching hospitals: Zale-Lipshy University Hospital, Parkland Memorial Hospital, Children's Medical Center, St. Paul Medical Center, and Veterans Administration Medical Center.
- Advertisements will be posted around campus and at the major clinical sites and hospitals.
- The study will be posted on the website Research Match.
- An advertisement will be sent out to all medical students, graduate students, postdoctoral scholars and allied health students using the campus list-server network.
- If further needed, a general advertisement will be placed in the Dallas Morning News to attract volunteers from the general public.

From the dropout rates seen in our previous studies, we have found that 94 patients are required to have 90% of patients (84) complete the study. Overall, we plan to generate the required number of patients within the first six months and allow these to enter the study such that smooth and continuous testing is maintained.

3.4 Bias Control Measures

3.4.1 Overview

In general, ethical and practical concerns of routine contact lens studies require that patients wear the same lens in each eye which corrects vision to acceptable levels (≥20/30 OU) for daily function.

3.4.2 Randomization

Following recruitment, test subjects will be randomized to either the DAILIES TOTAL1 or the ACUVUE TruEye. Lenses will be worn for daily wear over a 2 month time period. Following a second washout period, subjects will be fit in the second lens material (crossover arm) for an additional 2 month time period. Intersubject variation will be minimized by testing identical outcome measures with both lenses in the same eye of each patient.

3.4.3 Masking

Each sample obtained will be numerically coded. The clinical observer performing the eye irrigation and confocal microscopy will not know the specific lens test group. Since the methods of data collection are objective and standardized, outcome data samples will be analyzed independently in masked fashion.

3.4.4 Sample Size Determination and Statistical Methods

A total of 140 patients will be recruited for this study. Sample size calculations (detailed below) and statistical methods to detect significant changes in the outcome measures were derived from our previous studies evaluating the effects of silicone hydrogel lens wear on the corneal epithelium (Ladage et al, *Ophthalmology* 2001; 108: 1279-1288 and Robertson et al, *IOVS* 2008; 49: 7-15). The magnitude of change for of all outcome measures will be simultaneously compared between lens types using a Type I error rate of α=0.05. Statistical analysis will be completed in the Department of Clinical Sciences and Biostatistics at UTSWMC.

A. <u>Surface epithelial cell desquamation</u>

Surface epithelial cell desquamation is the most sensitive and reliable predictor of epithelial perturbation in response to contact lens wear. In our prior studies, silicone hydrogel lens wear worn in a daily modality reduced corneal surface epithelial cell desquamation by 40-50%. We hypothesize that the impact on epithelial shedding rate (cells/minute) will be less following wear of the Dailies Total 1 (delta ≤ 20% reduction) compared to wear of a standard silicone hydrogel daily disposable, the ACUVUE TruEye (delta ≥ 40% reduction). Assuming a difference in means between the two test lenses of 16.3 cells/minute and a standard deviation of 37 cells/minute, a total sample of 84 subjects in a 2x2 cross-over design will have 80% power at a significance level of α=0.05.

B. Drop outs

Additional subjects were added to compensate for the potential dropouts to satisfy the requirements for completion of the 6 month study. Based upon our previous clinical trials, we anticipate a dropout rate of 10-12%. In the absence of time, cost, and ethical concerns, Guo et al. (2013) suggested choosing the largest sample size to guarantee power for all 2 tests. Therefore, we will recruit a total of 94 subjects for this cross-over trial. That is, 47 subjects will be allocated to each sequence in this 2x2 cross-over trial.

Guo, Y., Logan, H., Glueck, D. & Muller, K. (2013), 'Selecting a sample size for studies with repeated measures', BMC Medical Research Methodology 13, 100.

4.0 PROCEDURES

4.1 Pre-randomization Testing

4.1.1 Eligibility Determination

All patients who wish to participate in the study and who meet the following screening criteria will be enrolled to ensure that 84 subjects complete the studies proposed:

- Age 18-38 years
- Myopia -1.00 to -6.00 with regular astigmatism (≤1.00 D OU)
- Habitual contact lens wearers able to wear lenses for a minimum of 8 hours daily or non-contact lens wearers wanting to try contact lenses
- No lens wear for one month prior to initiating lens wear. Patients must have a pair of eyeglasses with optimum spectacle correction in both eyes (funds are budgeted to provide this to patients who qualify and do not have glasses).
- No history or use of any systemic medications
- No history of ocular allergic disease
- No concomitant pregnancy or lactation
- Minority participation will be encouraged
- Charts of all existing and new contact lens patients seen by the contact lens clinic and MD faculty will be screened initially by the clinical coordinator, and possible subjects confirmed by the principal investigator (PI). Additional patients identified through our on campus recruitment methods will be similarly screened.
- Candidates who are felt to meet study requirements will be scheduled by the clinical coordinator for screening, a complete ocular examination and orientation.

Please note that an interview will be performed with the potential candidate in order to determine whether or not they meet the inclusion/exclusion criteria. Female patients will also be asked if they are pregnant or lactating. There will be a urine pregnancy test performed.

4.1.1.a Patient Orientation

The PI or her designate will explain to each subject all aspects of the proposed study with specific delineating of all possible risks, as well as derived benefits (see below: human subjects protection).

Key elements to be stressed include:

- Necessity for wear of corrective spectacles after all ocular irrigation procedures, including driving home afterwards.
- A need to complete the study voluntarily to receive a $140 allowance for frames and spectacle lenses (anything above the allowance to be paid by the participant), and a monetary bonus of $125. Involuntary termination, excluding non-compliance, will not result in loss of benefits.

4.1.1.b Comprehensive Ocular Examination

Volunteers who meet all criteria above, and who wish to participate in the study, will undergo a comprehensive ocular examination as follows: a single standard room (twenty-foot test lane within the contact lens service) and the same examining equipment will be used for all patients on all visits.

The examination will be performed sequentially as follows:

- **Snellen visual acuity testing (OU)**
  - This will be performed using a standard projector chart at twenty feet. All patients will be refracted to ensure that visual acuity and prescription are within the inclusion criteria.
- **Anterior ocular segment inspection by slit lamp examination**
  - Blink rate is estimated per minute OU
  - Normal eyelid and eyelash position is checked for both upper and lower lids OU
  - The tear meniscus is inspected and estimated for height in mm and presence or absence of cells and debris including mucous threads OU
  - The bulbar conjunctiva, cornea, anterior chamber, iris, and crystalline lens are inspected for any abnormalities OU
  - Meibomian gland orifices are inspected for signs of inflammation or plugging; eyelid skin margin is inspected for inflammation and scaling OU.
- **Aqueous tear production**
  - Following application of 1 drop of topical tetracaine OU, Schirmer test strips are applied to the lower fornix at the outer one-third of the lower eyelid for 3 minutes and the length of wetting recorded in mm (≥ 3.0 mm wetting/3 minutes considered within normal limits).
- **Corneal staining**

- One-drop of non-preserved isotonic saline is placed upon the tip of a fluorescein test strip and applied to the lower fornix with the patient looking up; presence or absence of corneal staining with fluorescein is then noted by the screening clinician.

- **Intraocular pressure measurement**
  - One drop of tetracaine is applied and the cornea is gently applanated with the tip of the Goldmann tonometer to ensure IOP ≤ 21 mmHg OU.
- **Evaluation of upper and lower eyelids**
  - Both upper eyelids are gently everted and both upper and lower conjunctival surfaces inspected for any abnormalities.
- **Fundus examination**
  - The pupil is dilated OU with 1 drop each of 2.5% neosynephrine and 0.15% mydriacyl applied 1x, X2, or x3 as needed at 10 minute intervals to achieve >5 mm dilation OU. The fundus is then inspected for the appearance of the optic nerve, macula, retinal vessels and periphery and any abnormalities noted. Any abnormalities are cause for non-inclusion.

4.1.1.c Subject Evaluation Assessment

Those subjects will be asked to begin the study who have:

- Met the inclusion/exclusion criteria listed above
- Expressed a willingness to participate after the initial explanation of all aspects of the study including but not limited to risk/benefit information
- Passed a comprehensive ocular examination (COE) without abnormalities
- Had the objectives, risks, benefits and all aspects of the study re-discussed with them by the PI, after the COE, with written informed consent finalized and signed by the patient for study inclusion and randomization to either test lens or control group.

4.1.2 Baseline Visit

One month after completing a successful COE, being enrolled in the study and randomized to a test group, patients will be scheduled for a baseline visit to the contact lens clinic for dispensing the assigned test lenses. Test lenses and their properties are summarized in Table II.

Table II: Test lens properties

Test Lenses	Material	Water Content	Dk*	Dk/t**	Base Curve
DAILIES TOTAL1	Delefilcon A	33%	140	156	8.50 mm
ACUVUE TruEye	Narafilcon A	46%	100	118	8.50 or 9.00 mm

*Dk: oxygen permeability, unit: $x10^{-11}$ $(cm^2/sec)(mL\ O_2/mL\ mmHg)$
**Dk/t: oxygen transmissibility, unit: $x10^{-9}$ $(cm/sec)(mL\ O_2/mL\ mmHg)$

At the baseline visit, all matters involving informed consent will be re-reviewed with the patient for the last time prior to lens fitting. The patient is given the opportunity to withdraw if desired.

4.1.2.a Brief pre-dispensing screening examination

Performed as for COE but Schrimer strip testing, IOP measurements and dilation are omitted

4.1.2.b Lens Fitting Procedures

- A Bausch & Lomb keratometer is used to measure the central corneal keratometry values in both eyes recorded to the nearest ¼ diopter ("K" value).
- Each eye will be trial fitted to ensure proper movement.
- Lenses will be checked for optimum comfort and final visual acuity (lens power).

4.1.2.c Lens Care Solutions

Since this trial is investigating daily disposable lenses, no lens care solutions will be required. Only preservative-free saline will be provided to rinse lenses prior to insertion.

4.1.3 Contact Lens Order and Adaptation

4.1.3.a Ordering Contact Lenses

The contact lens clinic will keep a computerized record file of lenses fitted by patient name and date filled and dispensed to the patient. Patients will be given the telephone number and contact person at this location (8 a.m. – 5 p.m., Mon-Fri) to obtain additional lenses if needed.

All lenses will be ordered and dispensed through the contact lens clinic. A log file of dispensed lenses will be maintained by the clinical coordinator.

4.1.3.b Dispensing and Training

Lenses will be dispensed in standard sterile packaging. Each patient will receive a minimum of one-half to one hour of "hands-on" training including:

- Lens insertion
- Lens removal
- Necessity for hand washing before handling lenses
- Use of only non-preserved, sterile saline rinses (no tap water)
- Wearing schedule: lenses must be worn for a minimum of 8 hours and no longer than 12 hours per day
- Need to document date and time of lens insertion and removal and the hours of comfortable of wear achieved on a daily basis. Documentation with reason will be

noted if lenses are not worn as prescribed and the study coordinator will be notified the same or next day (8 a.m. – 5 p.m.)

- Familiarity with a 24-hour emergency response telephone number (ophthalmology resident on call) to use with normal RSVP clinical rule: any change in Redness, Sudden alteration of Vision, or Pain – call and be examined without delay.

4.1.3.c Patient Adaptation and Contact Lens Check-ups

To ensure maximum patient safety, all patients will be required to achieve successful wear of test lenses. An overview of scheduled study visits with planned testing is given in Table 1. At each scheduled visit:

- Any subjective problems or complaints noted
- Visual acuity confirmed on Snellen chart at 20 feet in the standard test room
- A brief slit lamp assessment as outlined above performed
- Unscheduled (emergency) visits are covered below in section 4.3.2.c , *Unscheduled lens removal*

4.2 Randomization

Following recruitment, test subjects will be randomized to one of two sequences for the DAILIES TOTAL1 or the ACUVUE TruEye (see Table II). A randomization log will be created using SAS PROC PLAN with variable block sizes.

4.3 Post-randomization

4.3.1 Scheduling

- All post-randomization visits will be scheduled by the study coordinator. Required telephone numbers will be provided to patients.
- All visits will occur between 8 a.m. – 12 p.m. weekdays to control for time of day requirements when performing ocular irrigation studies. This will control for circadian effects on corneal epithelial cell shedding.
- Although every effort will be made to assess progress at the exact, fixed intervals specified, it has been found in our previous studies that small variations of 1-2 days do not influence the results in a significant way. Thus, this will permit some limited flexibility for patients to request a last-minute temporary alteration in scheduled testing in order to meet non-recurring urgent or emergency personal needs. This will be assessed on an individual basis with the PI as final arbiter.

4.3.2 Clinical Assessments

4.3.2.a Overview

Significant numbers of visits and complications are not anticipated. Since it is important not to disturb successful lens wear, brief clinical screening will be performed as detailed below.

4.3.2.b Clinical Screening Procedures

History: At each visit, the screening clinical observer will ascertain any history of (both eyes):

- Redness
- Visual change
- Pain
- Irritation
- Decreased wearing time with unscheduled lens removal
- Excessive lens movement or displacement

Screening exam

At each visit, the clinical observer will perform (Table III):

- Snellen VA measurement at 20 feet
- Slit lamp exam
- In the absence of any historical or clinical (objective) abnormalities, wear will proceed or experimental testing will be performed

Table III: Brief noninvasive clinical assessments for study visits 2-7.

1. Vision	Snellen distance acuity at 20 feet
2. Lenses	Position, movement, centration
3. Ocular surface	Bulbar conjunctiva Edema (0-4)* Vessels (0-4)* Exudates (0-4)* Cornea Edema (0-4)* Vessels (0-4)* Exudates (0-4)*
4. Anterior chamber	Cells (0-4)* Flare (0-4)*
*FDA grading scales of 0-4 as outlined in appendix A.2	

4.3.2.c Unscheduled lens removal

Patients are instructed to remove their lenses following the RSVP clinical rule: redness (irritation), sudden change in vision, or pain. They will then be examined as soon as they are able to come to the clinic on an emergency basis by calling the 24-hour telephone number (after hours) or the Contact Lens Clinic (8 a.m. – 5 p.m., Mon-Fri) to rule out serious complications of lens wear. Once the problem has resolved, the patient will be reinstated into the study. If lenses are removed for any reason of positive ocular findings (Table III above) by the clinical observer, or by the patient, the following additional steps will be taken.

- Fluorescein strip staining will be applied (as above) to determine if the corneal epithelium stains (punctate epithelial staining).
- If indicated, corneal infiltrates will be cultured in thioglycollate broth, and on chocolate and blood agar plates; Saboraud's media will be used additionally if fungus infection is suspected. The patient will be removed from the study and accordingly treated with antimicrobial therapy.

4.3.3 Laboratory Assessments

In general, laboratory assessment of each patient is performed sequentially as follows:

4.3.3.a Tear collection

Tear collection will be performed as the first clinical test. Three µl sample volumes tears will be collected non-invasively *in vivo* using microcapillary tubes from the inferior tear meniscus at the temporal canthus of both eyes. Tears will be collected with the patient seated at the slit lamp with the light on low illumination. Pooled tear samples will be placed in DNase free microcentrifuge tubes and briefly centrifuged at maximum speed to ensure all tears are at the bottom of the tube. Samples will then be maintained on ice while in the clinic and transferred to the -80˚ freezer for storage until processing. The procedure for tear collection and extracellular DNA quantification has been published elsewhere (Tibrewal et al, *IOVS* 2013). Extracellular DNA present on the posterior surface of the contact lens will be eluted in Tris-EDTA buffer and processed in parallel with the tear samples.

4.3.3.b Corneal epithelial cell collection

Corneal epithelial cells can be collected non-invasively *in vivo* using a custom-made ocular irrigation chamber specific for these types of studies. The corneal irrigation chamber collects corneal epithelial cells into a 15 ml test tube. The patient is seated with forehead resting against a headrest; a fixation target is placed to orient the eye to be irrigated downwards; and the irrigating tip is positioned 2 mm below the corneal apex. Irrigation involves the delivery of 9 ml of sterile saline to the central cornea for a period of 1 minute via a tubing pump (Cole-Parmer Instrument Co). By altering the distance from the irrigating tip to the corneal apex, a precise area of the ocular surface can be washed preventing contamination of conjunctival spillover. We and others have established the validity of this technique. Intersubject variation has likewise been established. Studies will be performed on left eyes of patients after lens

removal. Care is taken to count only corneal epithelial cells, which can readily be distinguished from conjunctival cells by size and nucleus to cytoplasm ratio (as previously published). The total shedding rate per minute is also attained.

4.3.3.c In vivo confocal microscopy

Details of the clinical use of this microscope are given in Appendix A.1.6. For these studies, a Heidelberg HRT confocal microscope engineered in house with remote controlled scanning capabilities will be utilized in the proposed studies (Petroll et al, *Cornea*, 2013). One drop of topical tetracaine will be placed in the subject's eye; the subject's head is then placed in the headrest as for regular slit lamp examination. Care must be taken to adjust the height of the chin rest to a comfortable level such that the patient can rest both feet flat on the floor to minimize movement. A drop of Genteal (Alcon Laboratories) is placed upon the top of the objective lens to serve as an immersion fluid. The cornea is then applanated using the standard tomocap objective lens tip. Both confocal microscopy through focusing scans and static images of the corneal epithelial surface will be acquired in the central cornea and in the temporal quadrant of the limbus by controlling for the patient's direction of gaze. Similar image sequences will be performed to sequentially image the upper eyelid at the midpoint of the eyelid (corresponding to the 5 and 7 o'clock position of the limbus). For upper lid imaging, the lid will be everted prior to image acquisition. Sequential imaging will allow for subsequent montage generation of the mid-point of the upper lid.

5.0 Human Subject Protection

5.1 Overview

5.2 Informed Consent

The consent form and protocol will be submitted to and approved by the Institutional Review Board (IRB) of the University of Texas Southwestern Medical Center. As both lenses are FDA approved, this will undergo an expedited study and we anticipate approval within a four week time period. Studies will commence upon approval. The investigator is responsible for ensuring that patients understand the intent of the investigation and their questions have been answered to their satisfaction before signing the Patient Informed Consent. The investigator is responsible for making sure each patient is aware of the time requirements and cooperation necessary on his/her part. The investigator will retain a copy of the consent form in the patient's file and a copy will be given to the patient.

5.3 Study Personnel

All personnel involved directly or indirectly in this study are trained and experienced professionals in the clinical care of contact lens patients. They are listed below with areas of major responsibility identified.

4. Danielle M. Robertson, O.D., Ph.D.
Dr. Robertson is a clinician scientist with a research interest in corneal cell biology, contact lenses and infection. As the principal investigator, Dr. Robertson will oversee the study in its entirety, including seeing patients, outcome measures assessment and analysis.

5. W. Matthew Petroll, Ph.D.
Dr. Petroll is a biomedical engineer with specific expertise in imaging. He has custom-built the HRT confocal microscope that will be used in the proposed studies. He will also provide expertise in data analysis.

6. Manali Shah, M.S.
Manali Shah is the clinical coordinator and will provide coordinating support for the project. She has considerable experience in clinical research studies, particularly those involving contact lens patients. She will be responsible for overseeing all patients recruiting, scheduling, monitoring, completion of forms, patient safety reporting and maintaining all records and study supplies.

7. Chul Ahn, Ph.D.
Dr. Ahn is the Director of Biostatistics at the UTSWMC. He has worked with Dr. Robertson on several previous clinical studies. Dr. Ahn will serve as the biostatistical collaborator on the proposed studies.

8. Aimee Tilley, B.S., COA
Aimee is research study coordinator who has also worked in the UTSW ophthalmology clinic as an ophthalmic technician and is a certified ophthalmic assistant.

5.4 Confidentiality

Patient records are maintained in strict confidentiality according to common clinical ethical usage and Federal and Texas state laws. Records are stored in high security areas in locked filing cabinets and are only accessible to professional personnel either associated directly with the study or with the need for emergency care on an after-hours basis. No records identifying the subject by name will be disclosed for any reason without specific execution of a written authorization by the patient. To protect confidentiality during data analysis and subsequent publication, database subjects will be identified only by lens group and an assigned confidential subject number.

5.5 Criteria for Discontinuing Contact Lens Wear

Lens wear will be discontinued by the patient on a temporary basis in accordance with the RSVP clinical rule (as defined above); and examined as soon as possible thereafter on a scheduled or 24-hour emergency basis. Following standard FDA contact lens protocol usage, an adverse reaction is defined as an unanticipated complication that might have been attributed to the use of the test lens or following testing (irrigation), and if untreated or ignored would have led to progressive or permanent reduction in visual acuity or resulted in sustained ocular damage; such occurrences will be reported promptly to the IRB and to the study sponsor.
In general, an adverse reaction, patient non-compliance, or patient choice will be the cause for discontinuance from the study. Major potential outcomes mandating discontinuance include:

2. The investigator will discontinue a patient at any time during the study for any reason if, in her opinion, it is in the best interest of the patient. The reason must be recorded.
3. A patient may voluntarily withdraw from the clinical trial for any reason. This reason must be recorded.
4. Discontinuation may be needed when the patient has not worn lenses for more than two days due to non-compliance.
5. Additionally, patients may need to be discontinued because of protocol deviations or because of lack of follow up or relocation. A patient is considered lost to follow up if a scheduled visit is missed and the patient is unresponsive to repeated attempts at rescheduling.
6. Patients will be discontinued if monitoring of the clinical trial reveals an unacceptable level of device related adverse events, even though some patients are not affected.

There are certain actions that are required for discontinued patients:

1. The investigator will perform an ocular examination and document the results and reason for discontinuation. Patients who have positive slit lamp findings that are at least one whole grade greater than baseline should be subsequently followed until their findings are stabilized and returned to baseline.
2. The investigational lenses must be retrieved from the patient. For relocated patients or those lost to follow up it must be documented that every attempt and effort was made to locate the patient and retrieve all investigational lenses.
3. Should a patient be discontinued because of an ocular complication or adverse reaction, visits must be documented until recovery of ocular health and full visual acuity has been achieved, if such can occur.

5.6 Safety Monitoring: Adverse Events

5.6.1 Serious Adverse Events

Any adverse event that is serious but not likely due to contact lenses, such as a retinal detachment or cardiac arrest, must be reported to the IRB and the study sponsor.

5.6.2 Adverse Device Effects (A.D.E.)

Adverse device effects are hazardous, sight-threatening conditions such as corneal ulcers, corneal abrasions > 2mm, corneal scarring, iritis, permanent loss of vision, and other ocular infections or inflammations. All grade 4 biomicroscopy findings, which could be associated with these conditions, are thus considered potential adverse reactions except grade 4 tarsal abnormalities.

Each potential adverse device effect must be reported by the investigator to the IRB immediately at 214-648-3060.

And submit within 3 working days:

- A potential adverse event form including detailed drawings
- CRP's, lenses worn and any solutions or lens cases that may have been used at the time
- Cover letter/report with diagnosis

To UTSWMC IRB

Then if the patient is discontinued – a written report is also required indicating the subsequent treatment and resolution of the condition for the patient's file.

5.6.3 Undesirable Side Effects (U.S.E.)

All grade 3 findings and grade 4 tarsal abnormalities are considered ocular complications. They are associated with non-sight threatening, reversible events that may require temporary discontinuation of lens wear, treatment, or additional follow-up visits. Examples include giant papillary conjunctivitis, marked dry eyes, blepharitis, allergic responses, and general irritation.

6.0 Data Management, Quality Assurance, and Analysis

Data management and quality assurance will be accomplished in the Department of Ophthalmology. Statistical analysis will be conducted in the Department of Biostatistics and Clinical Sciences at UTSWMC. Dr. Chul Ahn, Director of Biostatistics, will serve as the biostatistical collaborator on this study.

6.1 Form Management

Data entry forms will be prepared and stored in the Department of Ophthalmology. Masters will be maintained on file with a complete packet issued at randomization for the patient's file. The patient's master file with copies of all encounters to date will be kept in a secured area in

the clinical research office to maintain confidentiality. Only single encounter forms needed for specific visits or tests will be taken to the clinic or laboratory for data recording. These will be returned to the master file the same day of completion.

6.2 Data Entry and Storage

Data entry will be accomplished in the Department of Ophthalmology upon completion of a visit. The patient's master file containing all completed forms will be kept in the clinical research office under secure conditions. Weekly backups will be completed for the entire database. In order to protect the confidentiality of patients, data access will be denied to all but authorized personnel. This will be achieved by a password system for the datasets. Further, patient names and other sensitive data will be encrypted on all storage media. To further ensure confidentiality, data collected within the laboratory and data sent to the biostatistician will all be numerically coded.

6.3 Data Quality Assurance

Range and validity checks will provide monitoring of the data entry process. Technical measurements will be subject to random personal spot-checks by the PI on a regular basis to ensure data accuracy. Since all personnel listed in the study are already fully trained and experienced in the routine clinical fitting and experimental methodology, significant errors in data determination are not anticipated. Reports of the data as entered will be printed so as to provide a visual check against the data entry forms. Periodic audits will be conducted by the PI and the study coordinator to compare data as entered in the database with those of the paper data entry forms. Discrepancies will be noted, corrected immediately, and reviewed for common error that may be avoided by future training.

6.4 Data Analysis Procedures

Data analysis will begin with the extraction of data from the master database in ophthalmology. Range and validity checks and determination of validity of missing values will be a first step in analysis. Patient confidentiality will be assumed during data analysis in that the patient names will not be used but will be numerically coded. Data will be analyzed using an intent-to-treat approach.

Continuous demographic and baseline characteristics will be compared between the DAILIES TOTAL1 and the ACUVUE TruEye using Student's t-tests or Wilcoxon rank sum tests. Categorical demographic and baseline characteristics will be compared between the DAILIES TOTAL1 and the ACUVUE TruEye using Fisher's exact tests or Chi-square tests.

Data analysis will be specific to the objectives outlined below:

1. The primary experimental objective of this study is to characterize the effect of the DAILIES TOTAL1 compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye, on corneal epithelial cell desquamation. This effect will be assessed using a standardized ocular irrigation technique to measure:
    a. Rate of desquamation of corneal epithelial cells (cells/min).

In this cross-over trial, treatment effects and carryover effects on the rates of desquamation of corneal epithelial cells (cells/min) will be compared between two treatment groups using Student's t-tests in Rosner (2006), and ANOVA in Chow and Liu (2014). If the p-value is less than $\alpha = 0.05$ for surface epithelial cell desquamation, then the surface epithelial cell desquamation is considered significantly different between the two groups.

References:
Rosner B. (2006) Fundamentals of Biostatistics, 6th Edition. Thomson-Brooks/Cole.

Chow S and Liu J. (2014) Design and analysis of clinical trials: concepts and methodologies, 3rd Edition. Wiley.

2. The secondary experimental objective of this study is to evaluate the effect of wear of the DAILIES TOTAL1 on the central corneal epithelium compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye. This effect will be assessed using IVCM to measure:
    a. Area of surface epithelial cells within the central cornea (μm^2).

Same analytical methods as described above for the primary endpoint will be used for the analysis of the secondary endpoint.

3. Multiple exploratory aims will also be investigated. These aims will be used to evaluate the effects of lens wear on the biology of the limbal epithelium, lid wiper and changes in the extracellular tear content of DNA in response to wear of the DAILIES TOTAL1 compared to a control, high oxygen permeable silicone hydrogel daily disposable contact lens, the ACUVUE TruEye.
   These will be assessed by:
    a. Area of surface epithelial cells within the limbal region.
    b. Thickness of the central and limbal epithelium.
    c. Dendritic cell infiltration in the limbal region.
    d. Staining of the lid wiper region with sodium fluorescein and lissamine green.
    e. IVCM evaluation of the lid wiper surface.
    f. Quantification of extracellular DNA adherent to the posterior lens surface and in the post lens tear film.

Exploratory data analysis will be conducted for the analysis of the above variables. Descriptive statistics will be computed and used for the estimation of the sample size needed for a future large trial if the study results look promising.

Dr. Robertson will be responsible for the final review of data analysis.

Appendix

A.1 Measurement Procedures

A.1.1 Contact Lens Diary

To ensure compliance, all subjects will be given a contact lens diary at their dispensing visit. Subjects will be asked to record the time of lens insertion and the time of lens removal daily.

A.1. 2 Tear Collection

Procedure - all samples are collected from both eyes of human subjects after lens removal by a single, trained investigator. Tear collection will be performed as the first clinical test immediately following lens removal.

1) A special fire-polished capillary glass tube is used (Drummond Microcaps)
2) The subject's chin is placed comfortably in the chin rest of a Haig-Streit slit lamp under normal illumination.
3) The top of the capillary tube is applied to the temporal edge of the tear meniscus inferiorly.
4) Three microliters of tears will be collected without touching the lid, conjunctiva or cornea to avoid stimulating reflex tearing from each eye.
5) Right and left eye samples will be pooled in a DNase-free microcentrifuge tube. Similarly, DNA extracted from the right and left worn lenses will be pooled.
6) All tear samples will be collected by a single trained investigator, numerically coded at time of collection and masked to laboratory personnel.
7) Samples will be frozen at -80°C until use.
8) Total DNA levels in tear sample volumes taken from each pooled sample will be assessed using the PicoGreen ds DNA assay (Invitrogen, Carlsbad, CA).

A.1.3 Lid Wiper Staining

Fluorescein and lissamine green staining will be used to assess the upper and lower lid wiper in the left eye of all subjects after lens removal.

1) 2% unpreserved fluorescein and 1% lissamine green will be sequentially instilled onto the inferior palpebral conjunctiva of the left eye.
2) Three minutes following dye instillation, the upper eye lid will be everted using a cotton tipped applicator and LWE staining evaluated.
3) Fluorescein staining will be visualized using Cobalt blue illumination and a Wratten No. 12 filter (Kodak, USA). Lissamine green staining will be illuminated using white light. Staining will be imaged using a SONY digital camera mounted to the slit lamp.
4) Staining will be graded according to the horizontal linear area (length) and the sagittal height (width) as published by Korb et al, *Cornea* 2010. The individual grades for length and width will be averaged to a final grade for fluorescein and a final grade for lissamine green. The higher of the final fluorescein and lissamine green staining grades were used as the LWE severity according to the following scale:

Grade 0 = no LWE
Grade 1 = mild LWE, score of 0.25 – 1.0
Grade 2 = moderate LWE, score of 1.25 – 2.0
Grade 3 = severe LWE, score of 2.25 – 3.0

b. Severity: Grade 0 = absent; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe

Fluorescein and lissamine green staining will be used to assess the upper and lower lid wiper in

A.1.4 *In Vivo* Confocal Microscopy

In vivo confocal microscopy will be performed on left eyes after lens removal.

1) 1 drop of topical anesthetic (tetracaine) is placed in the lower cul-de-sac of the right and left eyes.

2) The patient is seated such that the head is comfortably placed in the microscope chin-forehead rest with no hypo-hyper neck extension, both feet are flat on the floor and both arms are allowed to rest on the microscope table.

3) The patient fixates on the wall (distance) or near (light) target with the right eye to provide good fixational acuity.

4) One drop of Genteal (Alcon Laboratories, Ft. Worth, TX) is placed on the applanating tip to couple the cornea to the objective. The microscope joystick is used to adjust the microscope in the x-y-z direction to ensure proper alignment on the central cornea.

5) The remote controller is used to scan through the full thickness cornea. Images will be acquired by live streaming during scanning. For assessments of limbal changes, including the presence of dendritic cells, the limbal epithelia will be applanated at approximately 3o'clock position. Patients will be instructed to change their direction of gaze to facilitate imaging. Similar methodology will be used for the lid margin, with eversion of the upper eyelid required. Scanning of the lid margin will be performed using sequential image capture of overlapping regions corresponding to the 5 o'clock position of the limbus to the 7 o'clock position.

7) Note that the patient can freely withdraw backwards at any time desired.

8) When enough good quality images have been obtained, the patient withdraws the head, and microscopy is terminated.

10) For measurements of surface epithelial cell size, cell borders will be manually delineated on screen using MetaMorph software and total area per cell determined.

11) Dendritic cells present in the limbus will be manually counted from 3D image stacks using MetaMorph software.

A.1.6 Exfoliated Cell Collection and Quantitation

Ocular irrigation will be performed on the left eyes after lens removal and after staining with fluorescein.

1) The patient will be seated with forehead resting against a headrest; a fixation target is placed to orient the eye to be irrigated downwards.

2) The irrigating tip is positioned 2 mm below the corneal apex.
3) Irrigation involves the delivery of 9 ml of sterile saline to the central cornea for a period of 1 minute via a tubing pump (Cole-Parmer Instrument Co., Chicago, IL).
4) Following irrigation, samples will be immediately fixed in 4% paraformaldehyde. This will be accomplished by adding 9 ml of 8% paraformaldehyde (Electron Microscopy Services) to the existing 9 ml of sterile saline containing exfoliated cells.
5) Samples will be mixed by gentle inversion and placed on ice until taken to the laboratory for analysis.
6) The fixed cell suspension will be passed through a syringe filter holder containing a 13 mm diameter, 5 µm pore size polycarbonate filter (Nucleopore) to collect cells.
7) Each filter is then washed and simultaneously stained by passing 10 ml of sterile physiological saline (0.9% NaCl, pH 7.2) containing 10^{-4} M acridine orange (Sigma) through the filter system.
8) After removal from the syringe holder, the filters are placed on microscope slides, allowed to air dry and heated to 80°C in an oven for 10 minutes; each filter is then re-cooled and restained by addition of 1 drop of 10^{-4} M acridine orange solution.
9) A Leica inverted fluorescent microscope (Heidelberg, Germany) with an epifluorescence attachment (510 nm dichroic mirror, 450-490 nm excitation filter; 520 nm barrier filter) is used to examine each tissue sample at 1000x magnification under oil immersion.
10) The total number of corneal epithelial cells on each filter is recorded. Note: direct visualization of all cells by fluorescence microscopy is required to eliminate any skin cells or other debris contaminants from the final data set.

A.2 FDA Slit Lamp Findings Classification Scales

FDA guideline: Premarket notification 510(k) Guidance Document for Daily Wear Contact Lenses, May 1994, page 64

A.2.1 Edema

Classification		Edema
0	**None**	No edema
1	**Trace**	Slight localized or generalized edema a. Dull glass appearance (slightly hazy appearance) of the corneal epithelium, OR b. Just detectable central corneal clouding (CCC) without distinct borders
2	**Mild**	Mild localized or generalized edema a. Less than 15 vacuoles (microcystic), OR b. Light density CCC. Borders distinct but visible only against pupil, OR c. Corneal striae (1 or more)
3	**Moderate**	Significant localized or generalized edema a. 15 - 50 vacuoles (microcysts), OR b. Very distinct borders on CCC, OR c. Multiple striae including folds in Descemet's membrane (black lines).
4	**Severe**	Advanced localized or generalized edema a. More than 50 vacuoles (microcysts) b. Epithelial bullae c. Epithelial sloughing

A.2.2 Corneal Neovascularization

Classification		Vascularization		
0	**None**	No vascular changes		
1	**Trace**	Congestion and dilation of the limbal vessels Single vessel extension <1.5 mm from the prefitting position		
2	**Mild**	Extension of vessels < 1.5 mm from the prefitting position		
3	**Moderate**	Extension of limbal vessels 1.5 to 2.5 mm from the prefitting position		
4	**Severe**	Segmented or circumscribed extensions of limbal vessels more than 2.5 mm inside the limbus, OR extension to within 3.0 mm of corneal apex.		
		Location (optional):		
		N Nasal	T	Temporal
		I Inferior	S	Superior
		C Circumferential	X	Other (describe)

A.2.3 Corneal Staining

Classification		Corneal Staining
0	**None**	No staining
1	**Trace**	Minimal superficial staining or stippling a. Central or generalized b. Peripheral including 3 - 9 o'clock staining, OR c. Dimpling associated with bubbles under lens, OR d. Trace superficial lens insertion marks or foreign body tracks
2	**Mild**	Regional or diffuse punctate staining a. Central or generalized, OR b. Peripheral including 3 - 9 o'clock staining, OR c. Mild abrasion or foreign body tracks
3	**Moderate**	Significant dense coalescent staining, corneal abrasion or foreign body tracks
4	**Severe**	Severe abrasions (greater than 2 mm diameter[1]), ulcerations, epithelial loss, or full thickness abrasion. Diagram and explain

A.2.4 Injection

Classification		Injection
0	**None**	No injection present
1	**Trace**	Slight limbal (mild segmented), bulbar (mild regional), and/or palpebral injection
2	**Mild**	Mild limbal (mild circumcorneal), bulbar (mild diffuse), and/or palpebral injection
3	**Moderate**	Significant limbal (marked segmented), bulbar (marked regional or diffuse), or palpebral injection
4	**Severe**	Severe limbal (marked circumcorneal), bulbar (diffuse episcleral or scleral), or palpebral injection

A.2.5 Tarsal Abnormalities

Classification		Tarsal Abnormalities
0	**None**	Uniform satin appearance of conjunctiva
1	**Trace**	Slight conjunctival injection without texture
2	**Mild**	Mild or scattered papillae/follicles <1.0 mm in diameter
3	**Moderate**	Significant papillae/follicles <1.0 mm in diameter, and/or conjunctival injection
4	**Severe**	Localized or generalized papillae/follicles >1.0 mm in diameter with or without marked injection

A.2.6 Other (List all reports by specific finding and grade by severity)

Examples include but are not limited to:

Classification		Tarsal Abnormalities
0	**None**	No other significant biomicroscopic findings
1	**Trace**	Minimal findings such as a tear film abnormality (debris or low tear break up time)
2	**Mild**	Mild findings such as: a. Few faint infiltrates b. Lens adhesion
3	**Moderate**	Significant findings such as: a. Infiltrates (multiple or dense) b. Iritis with minimal cells or flare c. Conjunctivitis or EKC
4	**Severe**	Severe findings such as: a. Marked infiltrates with overlying staining b. Iritis with marked cells and/or flare c. Corneal or conjunctival infection d. Corneal ulcer e. Recurrent erosion

A.3 Patient Instructions

ACTIONS AND INDICATIONS
Contact lenses are used for the correction of blurred vision due to light being out of focus in non-diseased and otherwise healthy eyes.

STUDY PARTICIPANT GENERAL DIRECTIONS

- Please read and understand all the warnings, daily checks, precautions, contra-indications and adverse reactions sections.
- Do not wear any other lenses and use only the solutions provided by your eye care practitioner specifically for this study.
- It is important that you attend all scheduled office visits and wear your lenses as prescribed.

LENS WEARING SCHEDULE

- Lenses will be worn only during waking hours. Non-preserved saline, provided by your eye care practitioner, may be used to rinse lenses prior to insertion. Upon removal, lenses will be stored in the appropriate vials until your next scheduled appointment. At no time will lenses be left in overnight or re-used on additional days.

WARNINGS

You must follow the verbal instructions given to you by your eye care practitioner and the information contained in these instructions about your contact lenses, lens care products, daily checks and precautions as this is essential for the safe use of contact lenses and lens care products. Ignoring and disregarding this advice could result in serious injury to the eye.

DAILY CHECKS

Why should I check my eyes?
Although daily wear contact lenses have been used for several years and there are many patients throughout the world wearing lenses in this manner, in appropriate use of daily lenses can result in a serious eye infection. Regularly checking your eyes and acting appropriately should you detect any problems will significantly reduce the risks involved with lens wear.

How should I check my eyes?
Ask yourself these questions:
- **Do my eyes LOOK as they normally do?**
- **Do my eyes FEEL as they normally do?**
- **Do my eyes SEE as they normally do?**

If the answer is no to any of these questions then you should take the actions described below in "**What should I do if a problem occurs**" to remedy the problem and more importantly to prevent the occurrence of a serious adverse reaction.

What should I look for?

Some of the signs and symptoms of developing problems with your contact lenses can be very subtle and your vigilance and prompt action are vitally important to reduce to a minimum the risks involved with contact lens wear.

You should specifically check for the following:

- **Redness:** A red eye indicates an irritated eye. You may not feel any discomfort so always check in the mirror. Compare the eyes - increased redness in one eye only is highly suspicious and needs to be evaluated by your eye care practitioner.
- **Watering:** This is typically associated with discomfort but not always. Is it occurring in both eyes?
- **Light Sensitivity:** Most contact lens wearers find their eyes are slightly more sensitive to light from the first day of wear. You may need to use sunglasses more often. Be cautious if you notice a sudden increase in the sensitivity of your eyes to light, especially if it occurs in one eye only.
- **Discomfort:** Never ignore times when your eyes and lenses have become less comfortable. Some things like a speck of dust or lint under the lens can be easily removed by sliding the lens onto the white of the eye or by removing, rinsing and reinserting the lens. More serious problems such as superficial damage to the cornea will cause a progressive increase in discomfort. The sooner this is assessed and treated the better.
- **Illness:** Feeling unwell can have an impact on how your eyes cope with the contact lenses. In general if you have an illness such as influenza or viral gastroenteritis, where the body feels very "run down" – it is best that you DO NOT wear your lenses.

What should I do if a problem occurs?

1. Remove your lenses
2. If the discomfort or problem stops look closely at the lens
3. If the lens is in any way damaged, DO NOT put the lens back on your eye. Return the lens to the storage case and contact your eye care practitioner
4. If the lenses have dirt, an eyelash or other foreign bodies on them, or if the problem stops and the lenses appear undamaged, thoroughly clean, rinse and disinfect your lenses before re-inserting them.

   Note: **You must only use the lens care products given to you by your eye care practitioner for this clinical trial.**

5. If the problem does not stop, or if it recurs when you replace the lens, immediately remove your lenses and contact your eye care practitioner

PRECAUTIONS

Many problems can be prevented by using your common sense and following good hygienic habits, avoiding hazards, and understanding the nature of your lenses and how they work. This is a **list of precautions** you must follow to prevent damage to your eyes or your contact lenses:

- Always wash and rinse your hands before you handle your lenses. Eye irritation may result if cosmetics, lotions, soaps, creams or deodorants come in contact with your lenses.
- Avoid using aerosol products such as hair spray while wearing your lenses. If sprays are used, keep your eyes closed until the spray has settled.
- Always follow the lens care system explained to you for this study.
- Always use fresh solution when rinsing lenses.
- Do not use saliva or anything other than the recommended solutions to wet your lenses.
- Never use tweezers or other tools to remove your lenses from the lens container.
- Do not touch the lens with your fingernails since this may cause damage to the lens.
- Do not swim with your lenses on your eyes.
- Avoid all harmful or irritating vapors and fumes while wearing your lenses.
- Always inform your employer that you wear contact lenses. Some jobs may require that you not wear contact lenses.
- **As with any contact lens, follow-up visits are necessary to assure your health.**
- **Always consult your eye care practitioner before using any medicine in your eyes.**

CONTRAINDICATIONS

Do not use your contact lenses when any of the following exist:

- Acute or subacute inflammation of the anterior chamber of the eye.
- Any eye disease, injury, or abnormality of the cornea, conjunctiva or eyelids that would affect the wearing of contact lenses.
- Any active corneal infection (bacterial, fungal or viral) or purulent production (pus).
- Insufficiency of lacrimal secretion (dry eyes)
- Corneal hyposthesia (reduced corneal sensitivity).
- Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses.
- Allergy to any ingredient in a solution used to care for your contact lenses.
- Any medication which is contraindicated.

ADVERSE REACTIONS

Adverse reactions are symptoms and problems which are either known to occur and have been reported with the use of soft contact lenses, or new and unexpected findings. In general these effects are both more severe and serious with the use of extended wear contact lenses. Additionally there are effects which are most frequently only associated with extended wear. Do not sleep in your lenses overnight or wear lenses continuously for more than the duration prescribed by your eye care practitioner.

The following adverse reactions have been reported:

- Discomfort or feeling something is in the eye (a foreign body)
- Corneal abrasion or ulcer (or a scraped area)
- Eye infection
- Stinging, burning, itching (irritation)
- Excessive watering of the eyes (tearing)
- Unusual eye secretions
- Redness of the eyes
- Reduced sharpness of vision (poor visual acuity)
- Blurred vision, rainbows or halos around objects
- Sensitivity to light
- Dry eyes
- Corneal swelling

Reactions most frequently associated with contact lenses include:

- **Acute "Red Eye" Reactions**
  The exact cause of this reaction is unknown. The eye is likely to experience considerable discomfort, redness and watering. This condition usually clears up with lens removal and leaves no permanent damage to the eye.

- **Corneal Infection**
  This can occur when the protective layer of the cornea is damaged (e.g. by a foreign body beneath the lens) and the wound becomes infected by microorganisms, some of which may be present in the normal healthy eye. A severe infection can result in scarring of the cornea which may affect vision if located in the center of the cornea. There have also been cases of patients suffering serious and permanent eye damage, including loss of the eye, following severe corneal infection. Corneal infection can occur with daily wear of contact lenses.

  When any of the above symptoms occur, a serious condition such as infection, corneal ulcer, neovascularization or iritis may be present which could result in blindness. Seek immediate professional identification of the problem and prompt treatment to avoid serious eye damage.