

The TFOS International Workshop on Contact Lens Discomfort: Report of the Subcommittee on Clinical Trial Design and Outcomes

Gary Foulks,¹ Robin Chalmers,² Nancy Keir,³ Craig A. Woods,⁴ Trefford Simpson,⁵ Richard Lippman,⁶ William Gleason,⁷ Debra A. Schaumberg,⁸ Mark D. P. Willcox,⁹ Isabelle Jalbert,⁹ and the members of the TFOS International Workshop on Contact Lens Discomfort

¹Department of Ophthalmology and Vision Science, University of Louisville, Wilmington, North Carolina

²Atlanta, Georgia

³CooperVision, Pleasanton, California

⁴School of Medicine (Optometry), Deakin University, Geelong, Victoria, Australia

⁵School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada

⁶R.P. Chiacchierini & Associates, Rockville, Maryland

⁷Foresight Regulatory Strategies, Inc., Wilmington, Massachusetts

⁸Moran Center for Translational Medicine, John A. Moran Eye Center, Department of Ophthalmology & Visual Sciences, University of Utah School of Medicine, Salt Lake City, Utah

⁹School of Optometry and Vision Science, University of New South Wales, Sydney, New South Wales, Australia

Correspondence: Mark D. P. Willcox, School of Optometry and Vision Science, University of New South Wales, Sydney, NSW 2052, Australia; m.willcox@unsw.edu.au.

See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

Submitted: September 3, 2013

Accepted: September 4, 2013

Citation: Foulks G, Chalmers R, Keir N, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the Subcommittee on Clinical Trial Design and Outcomes. *Invest Ophthalmol Vis Sci*. 2013;54:TFOS157-TFOS182. DOI:10.1167/iovs.13-13189

Keywords: contact lens, dry eyes, tears, discomfort

The goal of this report is to review previously published clinical trials addressing contact lens discomfort (CLD) to identify appropriate trial design and outcome parameters to guide future clinical research that will characterize and investigate possible causes of CLD. A further goal is to identify possible confounding features of clinical trial design and performance in order to reduce bias in conduct of future trials or analysis of data from those trials.

Scope of Report

A contact lens is a foreign body placed on the eye, albeit of compatible material and design, applied to patients with variable biologic risk factors that influence the degree of experienced symptoms. The design of clinical trials and selection of appropriate outcomes that allow examination of CLD should be determined with respect to the specific questions being asked and answered by a specific trial. For example, the duration of a clinical trial to determine the time required for adaptation to a contact lens could be short, but such a time frame is inadequate for evaluation of chronic or persistent episodic discomfort. Similarly, evaluation of care system-related CLD would require control of not only the care system to be evaluated but also the contact lens (material, design, fit, and wearing pattern). Evaluation of symptoms of CLD should be done with questionnaire instruments that probe

parameters of discomfort unique to CLD. For example, a symptom of “dryness” may be an appropriate outcome for CLD if qualified by features of timing, duration, severity, and relationship to lens wear.¹⁻³ If a validated questionnaire is not available for the particular trial design, then visual analogue scales or numerical rating scales of comfort (on 1-100 or 1-10 scales) can be used. Although most of the data gathered from the literature for this report is derived from trials involving soft contact lenses, the principles for clinical trial design also apply to rigid contact lenses.

The proposed evaluation of CLD is for primary discomfort during lens wear. There are clinical conditions that can be produced by prolonged lens wear resulting in discomfort, but these conditions are secondary. For example, giant papillary conjunctivitis can occur in response to contact lens wear and produces symptoms of CLD (perhaps due to mechanical irritation from the edge of the lens or buildup of biological material on the lens), but this conjunctivitis would be considered a separate entity from CLD.⁴⁻⁶

Recognition of the fact that there is great variation in patient acceptance or tolerance of any noxious sensation requires that some qualification of the degree of discomfort be made. Thus a psychometric assessment of enrolled study participants may be required for some clinical trials.^{7,8}

RESULTS OF PRIOR CLINICAL TRIALS

The CLD clinical trial subcommittee searched the PubMed database using the search term “contact lens discomfort” (last searched on January 25, 2013). We included interventional trials involving contact lens wear that collected information about ocular comfort or discomfort, even if this was not the primary aim or outcome of the study. We searched the reference lists of included studies for any additional studies not identified by the electronic search. Clinical trials of contact lens performance may be published in the non-peer-reviewed professional literature (e.g., *Contact Lens Spectrum* or *The Optician*). We did not search non-peer-reviewed literature or any conference proceedings.

A review of published clinical trials assessing CLD is summarized in Table 1.⁹⁻³⁹ These were published between 1999 and 2013 and enrolled 18 to 362 participants. Trials typically were small; only four enrolled 100 or more participants. These participants were followed for 15 minutes to 3 months. It is clear that most prior clinical trials were designed to evaluate performance of certain contact lenses or lens care solutions rather than the specific nature and etiology of CLD. As a result, their ability to elucidate CLD is modest due to inherent weaknesses in the chosen study design. Nonetheless, certain features of CLD can be distilled from those clinical trials. To date, investigations into CLD have primarily focused on sensation, with little attention given to the possible visual disturbance aspect of CLD.

Interventional trials have included examining the effects of lens fitting characteristics,¹³ lens type,^{9,14-17,23,28,29,32,34,35} lubricating^{10,12,18,19,21,23,27,29,30} and therapeutic^{12,26,39} eye drops, and lens care regimen.^{11,22,31,33,36-38} A common limitation of these studies is the poor control of confounding variables such as care regimen, prior lens wear, wear experience, and timelines of reporting symptoms. The extent of visual near tasks or computer/video terminal use should be quantified and characterized. Potential effects of concurrent medications, both topical and systemic, require evaluation, as well as effects of seasonal allergy and climate.

Outcomes and Predictive Factors

Discomfort can be described by a study participant in a clinical trial in various ways. The relative activation by the stimulus of subpopulations of ocular surface sensory fibers evokes different qualities of irritation and pain sensations (see the report of the Neurobiology Subcommittee).^{40,41} Most of this corneal sensory research has been conducted without contact lens wear, so the role of these various nociceptors in CLD is not well established. Dryness is a frequently described sensation of CLD in study participants with reduced tolerance for contact lens wear,¹⁻³ particularly of higher intensity later in the day of wear.^{1,2,42}

Subjective Outcome Measurement

Clinical scientists rely on information in the form of data, some relatively direct (e.g., visual acuity) and other data less so (e.g., feelings of ocular surface dryness). These latter outcomes are often regarded as outcome measures and dealt with as though they are numbers, although whether all of these numbers can be regarded as distinct measurements is still unclear.⁴³ This concern is particularly salient when we do not have direct access to what is being measured and the dimensions or units as well as scaling of the metrics are unknown. This is by no means unique to the vision sciences and occurs frequently in psychometrics⁴⁴⁻⁴⁶ and psychophysics.^{47,48}

Part of the problem with trying to develop and evaluate qualitative or descriptive measurements (so called latent variables) is that they may or may not represent the property being measured. Wearer experience of discomfort is influenced by multiple contextual factors, which adds to the complexity of measurement. When developing new instruments, it is important to consider content validity compared with an established reference, if possible.⁴⁹ If measurements are “the same” as a gold standard, this is an empirical demonstration that the novel metric is as good as the reference (this is not quite a calibration, but it demonstrates that the new and old measures map onto each other in some rational way). If such is not the case, the validity of the measurement needs to be demonstrated in a number of possibly less direct ways.⁴⁶ Distinct from the measurement of a one-dimensional sensation, a patient-reported outcome instrument attempts to capture the patient experience in a more aggregate form. These instruments often have many questions, but are validated to show that they relate to self-assessment of the severity of conditions and change in condition. Not many potential patient-reported outcomes instruments have been used to assess CLD in some quantitative way, and all but one have been tested in only subjects who were not wearing contact lenses. Table 2 summarizes this list.^{1,25,50-62} Only one of these instruments was directly designed to examine symptoms in contact lens wearers,²⁵ and it has recently been validated in a shorter iteration.¹

Generally the direct validation work for ocular surface symptoms has not been on lens wearers specifically and has been descriptive in nature; and there have been a few reports of use of a theory-based assessment of the measurements (all using Rasch Analysis). The only validated contact lens-related dryness symptom measurement tool at the present time is the CLDEQ or its short form, CLDEQ-8.¹ The CLDEQ was validated in 2002 as a measure predictive of a doctor's diagnosis of contact lens dry eye.²⁵ In its long form, it was shown to have a sensitivity of 83% and specificity of 67%.²⁵ Scoring of the CLDEQ-8 involves summation of the items. In the validation work, the ranges for CLDEQ-8 sum score at baseline according to the wearers' overall opinion of their habitual contact lenses was as follows: Fair 17.4 ± 8.7 , Good 13.7 ± 6.4 , Very Good 9.1 ± 4.7 , and Excellent 6.4 ± 3.7 . Thus, using the CLDEQ-8 assessment of the symptoms with habitual lenses may help determine wearers who would benefit from management of their CL-related discomfort, and scores of 13 or above should warrant clinical attention. This version's diagnostic accuracy has not been tested. (Note that the CLDEQ-8 is copyrighted by Indiana University for public use. The university requires only that the copyright be cited in any publication reporting results with the instrument.)

Further assessment of patient symptoms can be done with respect to onset and time course to determine when CLD is occurring. Contact lens discomfort at the beginning of the day, but improving over time with wear, may have a different etiology than CLD with an onset at the end of the day. A further useful measure may be the duration of comfortable lens wear. Evaluation of the frequency and intensity of symptoms should be accomplished using a questionnaire designed to better understand the frequency and intensity of CLD. If a daily diary is used or it is necessary to assess symptoms at a particular point in time, a 0 to 100 visual analogue scale (VAS) or 0 to 10 scales may be more appropriate until alternative metrics can be developed and properly validated.

Clinical Measures That May Describe CLD

In an attempt to assess a number of outcome measures that are not subjective but that may be predictive of CLD, a PubMed

Investigative Ophthalmology & Visual Science

TABLE 1. Assessment of Published Clinical Trials

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Comfort/Discomfort Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Open label, single group, uncontrolled ¹⁰	Preservative-free hypoosmolar (280 mOsm/L) copolymer, commercially available in Italy (Farmiga, Pisa, Italy); contains 0.2% hyaluronic acid and 0.2% tamarind seed polysaccharide, pH 7.4; 3 times daily on waking with no lens, early afternoon and before bed with lenses in Verbal and written instructions for using a no-rubbing, rinsing lens care regimen following the manufacturer's recommendations	CLD as measured by OSDI	OSDI > 12; tear breakup time (TIBUT) ≤ 10; Schirmer 1 > 10 mm	15	60 d	Weak; high risk of bias (uncontrolled; placebo effect very likely)
Crossover, investigator masked ¹¹		CLD as measured by OSDI	Habitual soft contact lens daily wear for at least the past 6 mo, asymptomatic and satisfied with the vision and comfort of the habitual lenses	72 (65 completed)	10-wk study: 1- wk accrual (adaptation) followed by 2- wk trial × 3 conditions with 1-wk washout between conditions	Weak; high risk of bias (nonvalidated secondary outcome measures, industry funded, bias due to inadequate randomization likely)
Open-label, parallel- group, randomized trial ¹²	Azithromycin: 1 drop to each eye twice a day for the first 2 d, then 1 drop daily for days 3–29 applied in the morning before contact lens application Visine for contacts: 1–2 drops 4 times a day for 29 d spaced by approximately 4 h on each dosing	Comfortable contact lens daily wear time (C/FB) at week 4 (average of days 23–29)	CLDEQ ≥ 2	50 (25 per arm)	4 wk (29 d)	Moderate; intermediate risk of bias (open label), unbalanced, comfortable wear times at baseline may have favored treatment arm)
Open label, single group, uncontrolled, crossover ¹³	Lotrafilcon A was worn, and fit was assessed by observer and by subjective comfort. 8.60 BC,* then 8.40 BC only if fit unsuccessful with 8.60 BC.	Objective assessment of fit and subjective comfort rate (1–10 scale) after 1 and 15 min (lens settling)	Habitual lens wearers	95 subjects (190 eyes), 49 eyes fitted with second lens	6-mo study but paper presents nondispensing fitting data only, 15 min	Weak; high risk of bias (data from 2 eyes of 1 subject considered independent; uncontrolled, unbalanced, industry funded)
Randomized, double- masked, contralateral study ¹⁴	Asymptomatic group: Focus Night & Day (CIBA Vision, Atlanta, GA) vs. Acuvue 2 (Johnson and Johnson Vision Care, Jacksonville, FL). Symptomatic group: Focus Night & Day vs. Acuvue 2 (Johnson and Johnson Vision Care) and Focus Dailies (CIBA Vision) vs. Proclear Compatibles (CooperVision, Pleasanton, CA).	Ocular comfort on 0–100 rating scale	Habitual lens wearers	39 subjects; 20 asymptomatic lens wearers and 19 symptomatic lens wearers	7 h	Moderate; moderate risk of bias (partly industry funded, no run-in prior to enrolment)

TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Randomized single masked, using deception as control ¹⁵	Habitual daily wear hydrogel lens wearers were refitted with Iotraficon A (Focus Night & Day; CIBA Vision) but told they were randomly assigned to wear either low-oxygen or high- oxygen permeability lenses and were "masked" to lens assignment.	Subjective comfort and dryness VAS (0-100)	Habitual lens daily wear with >4 y experience	87 (81 analyzed)	2 mo	Moderate; high risk of bias (open label, habitual lens wear preintervention control likely to favor intervention; analysis not intention to treat; care regimen a potential confounder; industry funded)
Randomized, contralateral, crossover study, open label ¹⁶	Hioxifilcon A lenses (extreme H ₂ O, copolymer GMA-HEMA), diameter 14.2 mm, base curve 8.6-mm, center thickness at 3.00 diopter 0.07 mm, 59% water content, Group 2, high- water nonionic, cast-molded daily wear with fortnightly replacements. Omafilcon A (Proclear Compatibles; CooperVision), diameter 14.2 mm, BC 8.2 or 8.5 mm, center thickness at 3.00 D 0.065 mm, 59% water content, Group 2, high-water nonionic, cast- molded. OPTIFREE Express (Alcon Laboratories) disinfection solution and Clerz Plus Lens Drops (Alcon Laboratories). Patient switched to hydrogen peroxide if solution problems suspected (number not specified)	CLDEQ (frequency and severity of dryness, discomfort, and blurry vision)	Previous diagnosis of mild to moderate dry eye or thinking one has dry eye or symptoms of dry eye AND either tear breakup time < 10 s, Schirmer 1 test \leq 5 mm, staining \geq 1, or bulbar redness	40	6 wk in each arm (crossover), 12 wk total	Moderate; high risk of bias (open label, habitual lens wear preintervention control; use of baseline habitual lens wear control may have favored treatment arms; no washout)
Study 1: multicenter prevalence study Study 2: uncontrolled, single-masked (subjects) intervention study ¹⁷	Study 1: NA Study 2: senofilcon A daily wear lens for 2 wk Continuing with habitual lens care unless advised by investigator (unspecified)	Discomfort: 4-point scale (never, infrequent, frequent, constant)	Problem contact lens patients: difference of >2 h between average and comfortable wear time OR frequent or constant discomfort or dryness symptoms on CLDEQ OR limbal or bulbar hyperemia \geq 2 OR corneal staining \geq 3	Study 1: 1092 Study 2: 257	Study 1: NA Study 2: 2 wk	Moderate; high risk of bias (no washout; trial short; comparison to habitual lens wear control subject to bias; questionable external validity)

TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Randomized, controlled (no treatment), investigator- masked clinical study ¹⁸	Unpreserved 0.9% sodium chloride (Hydrabak; Laboratoires Thea, Clermont- Ferrand, France) in both eyes 4 times a day for 21 d. All subjects used the same contact lens care solution (type unspecified).	Ocular comfort: 0–100 continuous VAS with anchors “excellent (lenses not felt)” at one end and “very uncomfortable (lenses cause irritation or discomfort)” at the other	Experiencing ocular discomfort (irritation, stinging, burning, or sensation of intermittent blurred vision), TBUT ≥ 10 s, Schirmer 1 ≥ 5 mm in 5 min in both eyes	50; 30 randomized to intervention, 20 to control	21 d	Weak; high risk of bias (no washout; trial short; comparison vs. baseline; lacking no-treatment control; confounders not measured)
Study 1: prospective cross-sectional (3 groups). Study 2: randomized, contralateral, open label, no- treatment control ¹⁹	Study 1: etafilcon A 8.5-mm base curve (Acuvue 1-Day; Johnson and Johnson Vision Care) Study 2: 20- μ L ReNu MultiPlus (Bausch & Lomb, Rochester, NY) rewetting drop	Ocular comfort: 0–50 continuous VAS	Study 2 Symptomatic: self- reporting of at least 1 symptom often or continually on Shippai Eye Study ²⁰ Dry Eye Questionnaire	60 (20 per arm)	Study 1: 10 h Study 2: 30 min	Strong; low risk of bias (no washout; primary outcome poorly described (anchors and descriptors not specified)
Single masked (subject), contralateral, no- treatment control ²¹	2 drops of sterile, isotonic, buffered, solution of carboxymethylcellulose (CMC), sodium chloride, boric acid, potassium chloride, calcium chloride, magnesium chloride, purified water and preserved with PURITE (stabilized oxychlorocomplex) 0.005% (Refresh Contacts; Allergan, Inc., Irvine, CA) on back surface of contact lens prior to insertion vs. straight from packaging in contralateral eye	Ocular comfort on 0–100 rating scale	At least 1 mo of lens wear Symptomatic lens wearers based on answering “no” to “Are you able to wear your lenses for as long as you want?”	61 (59 analyzed): 12 symptomatic, 49 asymptomatic	8 h	Weak; high risk of bias (2 authors employed by industry; investigator not masked; no washout; unequal arms; analysis not ITT; some data [e.g., comfort] not presented)
Crossover, single masked (investigator) ²²	OPTI-FREE Express Lasting Comfort No Rub Formula (Alcon Laboratories) vs. ReNu MultiPlus (Bausch & Lomb)	Comfort (0–100 VAS)	At least 1 y of lens wear, 8 h/d	8	4 wk	Weak; high risk of bias (no washout; not randomized; sample size too low; confounders not controlled [e.g., lens type])

TABLE 1. Continued

Study Design (e.g., Placebo-Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Multisite, uncontrolled, open label ²³	Nelfilcon A containing high molecular weight, nonfunctionalized polyvinyl alcohol (PVA) and packaging saline containing hydroxypropyl methylcellulose and polyethylene glycol (Triple Action Moisture DAILIES AquaComfort Plus; CIBA Vision) worn daily on daily disposable schedule	Frequency and severity of 8 common subjective symptoms (tired eyes, irritated eyes, lens awareness, blurred vision, redness, discomfort, deposits, dryness)	Contact lens wearer reporting at least 2 symptoms often or always	83 (81 completed)	4 wk	Weak; high risk of bias (use of baseline habitual lens wear comparison may have favored treatment arm; no washout; industry sponsored, conducted, written)
Randomized, controlled, double-masked, single-center clinical trial ²⁴	3-mo absorbable glycolic acid and trimethylene carbonate punctal plug (EXTEND Absorbable Synthetic Implants; Odyssey Medical, Memphis, TN) vs. sham procedure	CLDEQ	Symptomatic dry eye contact lens wearers with CLDEQ score > 0.13 ²⁵	32 enrolled, 22 eligible based on CLDEQ score, 19 completed	6 wk	Strong; low risk of bias (sham procedure and blinding well described; regression toward the mean and placebo effect likely)
Randomized, investigator masked, placebo controlled ²⁶	Cyclosporine 0.05% ophthalmic emulsion (Restasis; Allergan, Inc.) twice per day vs. rewetting drops (carboxymethylcellulose 0.5%, Refresh Contacts; Allergan, Inc.), twice per day, to be used before and after lens wear	Subjective evaluation of dryness severity (mild, moderate, severe), OSDI	Self-reported history of contact lens dryness/intolerance	17	5 wk	Medium; moderate risk of bias (patients unmasked; subjective bias likely); demographic data not provided
Randomized, double masked, placebo controlled ³⁹	Cyclosporine 0.05% ophthalmic emulsion vs. Refresh Preservative Free Artificial Tears (Allergan, Inc.) twice a day	OSDI and National Eye Institute Refractive Error Quality of Life Instrument	Chart review to identify contact lens wearers with complaints of dryness including irritation, burning, decreased wearing time	44 (22 per arm)	3 mo	Strong; low risk of bias (continuing use of habitual lens and cleaning regimen potential confounder; no washout)
Randomized, double-blind, parallel-group 15-center study ²⁷	2% polyvinylpyrrolidone (PVP) vs. 0.9% NaCl 1–6 drops per day as required	Overall contact lens comfort (VAS scale)	Contact lens wearers complaining of discomfort and soreness, irritation, smarting, burning, blurred vision aggravated by environmental factors (air conditioning, heating, working conditions, e.g., prolonged use of visual display unit)	45 (25 PVP, 20 NaCl)	28 d	Weak; high risk of bias (unbalanced; industry sponsored, conducted, written; variable dosage confounder)

TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Single-center, double-masked, randomized, crossover, pilot clinical trial ²⁸	Senofilcon A (Acuvue Oasys with Hydraclear Plus; Johnson and Johnson Vision Care) vs. habitual (control) during 75-min controlled adverse environment (CAE) exposure	Ocular discomfort (0–4 scale)	Soft contact lens wearers with histories of ocular discomfort during lens wear in windy or dry environments	11	75 min	Weak; high risk of bias (use of habitual lens wear control a potential confounder; inadequate sample size; masking not described; industry funded)
Randomized, contralateral, crossover, open- label clinical trial ²⁹	Intervention 1: etafilcon A (1-DAY Acuvue; Johnson & Johnson Vision Care) vs. lotrafilcon A (NIGHT & DAY; CIBA Vision) Intervention 2: NaCl 90 mg/mL (AstraZeneca, North Ryde, NSW, Australia) vs. PVA 14 mg/mL, povidone 6 mg/mL, sodium chloride (Refresh; Allergan, Inc.) vs. carboxymethylcellulose (CMC) 5 mg/mL (Cellufresh; Allergan, Inc.) every 2 h for 6 h	Comfort (100-point scale)	At least 12 mo of lens wear fitted	15	6 h on 4 separate days	Moderate; moderate risk of bias (patients masked for lens type but unmasked for drop type except at insertion; investigators not masked)
Prospective, single- masked (subjects), randomized, crossover study ³⁰	Lotrafilcon A with hypoosmotic (280 mmol/kg) vs. hyperosmotic (380 mmol/kg) saline 15 μ L 4 times a day	Comfort (1–100 scale)	Symptomatic lens wearers with maximum comfortable wearing time < 6 h	15	6 h	Strong; low risk of bias (investigator not masked)
Randomized, double-masked, 19-site study ³¹	OPTI-FREE Replenish (Alcon Laboratories) vs. ReNu MultiPlus No Rub Formula (Bausch & Lomb)	Comfort and dryness scores (0–100 scale)	Symptomatic wearers of group IV soft lenses answering disagree or strongly disagree to “My contacts are comfortable all day long” and agree or strongly agree to one or both of “During the day, I take my contacts out earlier than I like because they become uncomfortable” and “Late in the day, my contacts become uncomfortable but I continue wearing them”	362 (183 OPTI- FREE vs. 179 ReNu MultiPlus)	28 d	Medium; moderate risk of bias (no washout; lens type solution interactions likely confounder)

Investigative Ophthalmology & Visual Science

TABLE 1. Continued

Study Design (e.g., Placebo-Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Randomized, crossover study, open label ³²	Omafilcon A (Proclear; CooperVision) vs. new habitual lenses (control)	Subjective symptoms VAS (10 cm) scale (comfort and dryness severity; dryness, eye irritation, itchiness, burning, soreness, scratchiness, grittiness, watering, light sensitivity frequency)	Contact lens wearers with dry eyes (NEI definition: Schirmer without anesthesia \leq 5 mm, rose bengal staining \geq 3, fluorescein staining \geq 3, meibomian gland dysfunction \geq 2)	76	6-wk crossover	Weak; high risk of bias (open label likely to favor new lens type; use of more than 1 lens type as control a confounder; industry funded)
Randomized, double-masked, crossover over study ³³	Lotrafilcon B with polyhexamethylene biguanide (PHMB) (Solocare Aqua; CIBA Vision) vs. PHMB with surfactant (Hydro Health, Disop, Spatin) solutions	10-item symptoms questionnaire (0–10 scale); discomfort; blurry vision, lens-handling problems, dryness, redness, tearing, burning, itching, discharge, dissatisfaction + CLDEQ	Daily wear of lotrafilcon B for $>$ 3 mo	54	1-mo crossover	Strong; low risk of bias
Randomized, crossover, single masked (participant) ³⁴	5 silicone hydrogels: galyfilcon A (Acuvue Advance; Johnson & Johnson Vision Care); senofilcon A (Acuvue OASYS; Johnson & Johnson Vision Care); lotrafilcon B (O ₂ Optix; CIBA Vision); lotrafilcon A (NIGHT & DAY; CIBA Vision); balafilcon A (PureVision; Bausch & Lomb) disinfected with ClearCare (AOSEpt Plus; CIBA Vision) for $>$ 6 h	Comfort, burning, dryness, analogue scales (0–100) with verbal anchors at various times (insertion, settling, 8 h, 12 h on days 1, 4, 7, 10, and 14 using handheld wireless communication devices)	Adapted soft lens wearers	55 (45 completed and analyzed)	4-wk crossover with 1 d washout	High; low risk of bias (base curve selection for 2 of 5 lens types a potential confounder; single masked only)
Retrospective multistudy, multicenter analysis, open label, uncontrolled ⁹	Lotrafilcon A (NIGHT & DAY; CIBA Vision) or lotrafilcon B (O ₂ Optix; CIBA Vision) daily wear or continuous wear	Dryness during the day and end-of-day from CLDEQ	Adapted soft lens wearers (nonsilicone hydrogel)	259	2 wk (lotrafilcon B) or 1 mo (lotrafilcon A)	Weak; high risk of bias (open label; subject masked to study sponsor only, not to lens type; retrospective; uncontrolled; multiple wear schedule and lens type a confounder)

TABLE 1. Continued

Study Design (e.g., Placebo-Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Contralateral, randomized, double masked ⁵⁵	Etafilcon A (Acuvue; Johnson and Johnson Vision Care) vs. Omafilcon A (Proclear Biocompatibles; CooperVision)	Subjective comfort and dryness (100-mm VAS scale with anchors at 0 = very dry and 100 = no dryness) at 0, 1, 3, 5, and 7 h	Symptomatic: Wearers with symptoms of dryness after 5 h of wear with consequently reduced wearing time and use of lubricating drops at least once daily Asymptomatic: wearers without symptoms of dryness or discomfort who could wear lenses all day without use of lubricants	40 (20 symptomatic, 20 asymptomatic)	7 h	Moderate; moderate risk of bias (no washout; contralateral eye effect potential confounder)
Randomized, investigator-masked, crossover study ³⁶	Hydroxypropyl methylcellulose (HPMC) (COMPLETE ComfortPLUS; Allergan, Inc.) vs. citrate (No Rub OPTIFREE Express; Alcon Laboratories) solution with fresh habitual lenses	Daytime and end-of-day comfort and dryness (50-point continuous scale with anchors 0 = impossible to wear and 50 = excellent)	Experienced daily lens wearers	75 (64 completed)	1-mo crossover with 1-wk washout	Moderate; moderate risk of bias (participants masked only to study sponsor; lens type confounder; industry funded)
Retrospective, 7-site open-label trial ³⁷	Senofilcon A (Johnson & Johnson Vision Care) daily wear with multipurpose solution (MPS) (one of Polyquad/EDTA, Alcon Laboratories; Polyquad/nananoyleDTA, Alcon Laboratories; PHMB/borate, Bausch & Lomb; PHMB/phosphate, CIBA Vision) vs. hydrogen peroxide (H ₂ O ₂) vs. daily disposable (DD)	Comfort and dryness on a 1–10 scale with anchors 1 = poor and 10 = excellent	Previous wear experience not specified	283 (160 MPS, 83 H ₂ O ₂ , 40 DD)	3 mo	Weak; high risk of bias (open label; not randomized; retrospective; multiple MPS and replacement schedule confounders; unbalanced; same participants in more than 1 trial)
Randomized, investigator-masked, 2-site crossover study ³⁸	No Rub OPTIFREE Express (Alcon Laboratories) vs. Complete (Allergan, Inc.) or ReNu MultiPlus (Bausch & Lomb) with Acuvue 2 (Johnson and Johnson Vision Care) or Soflens 66 (Bausch & Lomb)	Subjective preference based on answer to "Did you notice a difference in comfort provided by the study solutions?"	Daily wearers	89 (47 and 42 at each site); 71 completed	2-mo crossover with 72-h washout	Weak; high risk of bias (participants not masked; unequal group sizes; randomization not stratified by site)

For many studies attracting good overall quality rating, a subjective contact lens comfort improvement was found in both the treated and the placebo groups.^{27,33}

* BC, base curve.

TABLE 2. Candidate Outcomes for Clinical Trials

Name, Reference	Validation With a Contact Lens-Wearing Population
Developed for contact lens wear	
Contact Lens Dry Eye Questionnaire (CLDEQ) ²⁵	Yes; screening
CLDEQ-8 ¹	Yes; screening and responsiveness
Contact Lens Impact on Quality of Life (CLIQ) ⁵⁰	Yes; quality of life; keratoconus only
Developed for dry eye without contact lenses	
Dry-Eye Questionnaire (DEQ) ⁵¹	No
DEQ ⁵²	No
Ocular Surface Diseases (OSD) questionnaire (in French) ⁵³	No
Impact of Dry Eye on Everyday Life (IDEEL) questionnaire ⁵⁴	No
McMonnies ⁵⁵	No
Ocular Surface Disease Index (OSDI) ⁵⁶	No
Symptom Assessment in Dry Eye (SANDE) ⁵⁷	No
Subjective Evaluation of Symptom of Dryness (SeSOD) ⁵⁸	No
Short questionnaire for dry eye syndrome (DES) questionnaire ⁵⁹	No
Unnamed questionnaire (in Spanish) ⁶⁰	No
Standard Patient Evaluation of Eye Dryness (SPEED) ⁶¹	
Texas Eye Research and Technology Center (TERTC) ⁶²	No

literature review was conducted using the search terms “comfort AND contact lenses” with the addition of search terms related to the outcome. The Subcommittee on Clinical Trial Design and Outcomes agreed in advance to investigate a number of outcome measures that fall under the broad categories of staining, hyperemia, tear film changes, vision, ocular sensitivity and contact lens surfaces. The resulting relevant manuscripts were reviewed and evaluated for standardization and agreement. There is a large volume of work reporting on contact lens outcomes, and so a representative list of studies investigating CLD is presented in Table 3. A few “other” assessments/responses to contact lens wear are also described in this section.

Staining of the Cornea. Staining of the cornea is an established method of evaluating the ocular surface.^{37,38,63-72} For corneal staining, sodium fluorescein is generally used, and methods for instillation and observation have been reported.^{73,74} Corneal staining is often measured in studies evaluating CLD; however, it has been reported to be a frequent outcome that is not well understood.^{74,75} With respect to grading corneal staining, there are various systems in use; however, only some have been validated for precision and reliability, such as the Efron scale and the Cornea and Contact Lens Research Unit (CCLRU) scale.⁷⁶ Information related to corneal staining can include its severity, type, and location, which can be used to help identify the etiology for the staining and may be important to understand its impact on CLD. Diffuse staining, when people use daily wear of lenses with multipurpose disinfecting solutions, in a characteristic annular pattern across the entire cornea or concentrated in three or more peripheral quadrants, has been described as solution-induced corneal staining (SICS),⁷⁷ also known as preservative-associated transient corneal hyperfluorescence.⁷⁸ This is quantified mainly on the extent (or % corneal coverage) of corneal staining.^{69,79,80}

Of the studies reviewed, investigations typically compare corneal staining at baseline to staining at follow-up visits, subsequent to an intervention with one or more contact lens types or lens care systems. Baseline visits often occur following a “washout” period of no lens wear or earlier in the day prior to lens insertion. Studies investigating SICS have performed measurements at baseline, then after 2 to 4 hours of lens wear,^{65,79} and then again at the end of the day.

As indicated in Table 3, corneal staining may be related to CLD; however, there have been mixed reports in the literature. The location and type of corneal staining may be important for different aspects of contact lens performance.

It is recommended that studies report method and techniques used to assess staining and that a common grading system be adopted to aid in the interpretation of staining across studies. Grading methodology, such as the methodology proposed in the report of the National Eye Institute and Industry-Sponsored Dry Eye Workshop,⁸¹ may not be adequate to grade corneal staining observed with contact lens wear. With respect to SICS, a better understanding of the uptake and release profiles of excipients in the disinfecting solutions with contact lenses may aid in study design, particularly with respect to determining the optimal times for clinical assessments to be conducted. In fundamental studies, where certain lens characteristics, lens care systems, or other variables are altered, controlling as many other factors as possible is warranted to better understand the relationship between corneal staining and CLD.

Staining and Indentation of the Bulbar Conjunctiva. Changes in the bulbar conjunctiva occur with CL wear.^{71,82-85} Either sodium fluorescein or lissamine green dyes are typically used for the assessment of conjunctival staining; however, lissamine green has been reported to be better at differentiating symptomatic from asymptomatic contact lens wearers.⁸⁴ A number of different grading scales have been used, such as the Efron scale⁸⁶ and the CCLRU scale.⁸⁷ Other scales developed for evaluation of dry eye include the National Eye Institute/Industry Workshop scale,⁸¹ the TFOS Dry Eye Workshop scale,⁸⁸ and the Sicca scale⁸⁹; but these have not been validated for evaluation with contact lens wear. It is recommended that the type of conjunctival staining, such as lens edge-related conjunctival staining^{82-84,90,91} or diffuse conjunctival staining, be specified. As indicated in Table 3, conjunctival staining and indentation may be associated with CLD.

Staining and Roughness of the Palpebral Conjunctiva. Korb et al.⁹² introduced the term “lid wiper” to refer to the area of the upper eyelid that spreads tears over the surface of the cornea (or contact lens) and the term “lid wiper epitheliopathy” (LWE), which refers to the disruption of epithelial cell integrity in this area. A similar area in the lower

TABLE 3. Clinical Measures of CLD

Outcome	Associated With CLD?	Methods	Key Findings
Corneal staining	Yes	Data obtained from 7 prospective trials, $n = 283$; 4 groups wore senofilcon A lens material on a daily-wear basis using multipurpose solutions (DW-MPS, $n = 160$), 2 groups using hydrogen peroxide (DW-H ₂ O ₂ , $n = 83$), and 1 group wearing the lens on a daily disposable basis ($n = 40$). Participants were followed for 3 mo using the same protocol.	Comfort at insertion and end of day, and end-of-day dryness scores, were significantly lower for participants who experienced solution-induced corneal staining (SICS; 8.2 ± 1.6 , 7.0 ± 1.9 , and 7.0 ± 2.2) than for those who did not (8.8 ± 1.2 , $P = 0.004$; 7.9 ± 1.7 , $P = 0.002$; and 7.9 ± 1.8 , $P = 0.003$, respectively). ³⁷
	Yes	Ninety-day, randomized, concurrently controlled, double-masked, multisite study involved 573 subjects at 30 investigational sites in the United States, using 1 of 2 multipurpose disinfecting solutions.	Differences noted in the level of corneal staining (SICS) between the 2 disinfecting solutions, and the solution that gave most SICS was rated worse for subjective comfort (insertion, removal, overall). ⁶⁶
	Yes	Retrospective analysis of a series of open-label studies conducted with 24 groups of approximately 40 participants, each wearing 1 of 6 silicone hydrogel contact lenses with 1 of 4 lens care products bilaterally for 3 mo of daily wear.	Participants with SICS had lower levels of comfort during the day (7.9 ± 1.7 vs. 8.5 ± 1.4 , $P = 0.03$), comfort at the end of the day (6.6 ± 2.1 vs. 7.4 ± 1.9 , $P = 0.03$), overall dryness (7.4 ± 1.9 vs. 8.0 ± 1.7 , $P = 0.04$), dryness at the end of the day (6.7 ± 2.2 vs. 7.5 ± 2.1 , $P = 0.01$), feelings of burning and stinging (8.5 ± 2.0 vs. 8.9 ± 1.8 , $P = 0.02$), and overall vision (8.2 ± 1.6 vs. 8.7 ± 1.3 , $P < 0.001$). ⁶⁴
	Yes	Two sites conducted a randomized, investigator-masked, 2-mo crossover study; $n = 45$ used regimen 1 and 2 for 1 mo each (study 1), and $n = 44$ used regimen 1 and 3 for 1 mo each (study 1). 1 of 2 soft lens types was randomly assigned, and the same lens type was worn throughout the study.	Significantly more subjects preferred the comfort of an MPS that gave low levels of corneal staining (SICS) (61.8%) to that of regimen 3 (11.8%). ³⁸
	Possibly	One-week, daily-wear, subject-masked, bilateral, parallel-group study with subjects ($n = 282$) randomly assigned to 1 of 2 daily disposable soft contact lenses.	There was a weak correlation between corneal staining and comfort for 1 lens ($r = 0.27$, $P = 0.002$, $n = 136$), but not the other ($r = -0.11$, $P = 0.18$, $n = 140$). ⁷⁰
	Possibly	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a polyhexamethylene biguanide (PHMB)- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; corneal staining.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, or burning or stinging. However, grittiness or scratchiness was higher with PHMB-containing system, and so were the level and extent of corneal staining (SICS). ⁷¹
	No	Prospective, bilateral, single-masked (investigator), randomized crossover design with 4 phases (1 for each care system). Each study phase comprised 2 consecutive days of lens wear on which the lenses were inserted on day 1 directly from the blister-packs and worn for over 8 h, then inserted on day 2 after overnight disinfection with 1 of the study lens care systems. $N = 25$ adapted soft contact lens wearers who were able to wear their habitual lenses comfortably for more than 12 h were recruited.	Even though 1 MPS was associated with high levels of corneal staining (SICS), there was no difference between the lens care systems and subjective comfort over a 2-d period. ⁶³
	No	Three-month prospective study; $n = 120$ participants were randomized into 1 of 3 lens types (etafilcon A, narafilcon A, and senofilcon A), all worn bilaterally on a daily disposable regimen; observations were at baseline, 2-wk, and 1- and 3-mo visits.	No differences were found between lenses in the 1-100 rating scale ($P > 0.05$) even though some lenses had statistically worse corneal staining. ⁶⁴
	No	A series of pilot studies using a total of 27 subjects (some of whom were enrolled in 2 or more studies) was conducted over 11 mo using a double-masked, randomized, crossover design. Asymptomatic, adapted, daily-wear soft lens users were included; evaluations were at baseline and after 1 and 2 h of wear.	Significantly increased extent of corneal staining (SICS) was observed at 2 h when subjects used silicone hydrogel lenses soaked an MPS, but significant levels of symptoms were not correlated with extent of staining. ⁶⁵

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
	No	Prospective, double-masked, single-investigator study; $n = 20$ participants were recruited for 2 visits with lenses worn bilaterally for 2 h.	Comfort scores did not differ between eyes ($P > 0.05$) despite significantly less corneal staining (SICS) in 1 eye compared to the other. ⁶⁸
	No	Double-masked, randomized, 1-mo crossover study; $n = 50$ adapted soft lens wearers.	Significantly different ($P < 0.01$) levels of relatively asymptomatic corneal staining (SICS) were observed with 1 lens care solution (37%) compared to the other (2%); symptoms were not correlated with the degree of staining. ⁶⁹
	No	Observational study; $n = 50$ (19 men, 31 women; mean age, 32.1 ± 11.4 y) adapted lens wearers. Comfort was evaluated using the Contact Lens Dry Eye Questionnaire. Corneal staining was assessed in the right eyes. Nonparametric analyses were used to study differences between groups and correlations between objective tests and symptoms.	No difference in corneal staining observed between asymptomatic and symptomatic lens wearers. ⁷²
Conjunctival staining	Yes	The study was conducted on a cohort population of 27 established soft contact lens wearers, who wore each contact lens type, in a random order, for a period of 10 (± 2) days. Circumlimbal staining was measured in a double-masked fashion through image analysis of digital photographs of lissamine green taken under controlled experimental conditions.	An inverse association between circumlimbal staining and contact lens comfort was demonstrated. Lenses with a rounded edge design produced the lowest comfort (72 of 100) whereas lenses with a knife-edge design produced the highest (87 of 100). ⁸²
	Yes	Overall staining, as well as staining at 5 separate sites (limbal, nasal band, temporal band, superior, and inferior), was graded on an analogue scale in 48 contact lens-wearing subjects and 50 control non-lens wearers. The degree to which subjects experienced sensations of dryness, wateriness, itchiness, grittiness, and comfort was also assessed using analogue scales.	In regression analysis, overall conjunctival staining was associated with the degree of dryness and the amount of itchiness. ⁸³
	Yes	Lissamine green and sodium fluorescein conjunctival staining were assessed in 102 soft contact lens wearers and 79 non-contact lens wearers.	Lissamine green staining (\geq grade 1) could discriminate symptomatic from asymptomatic lens wearers ($P = 0.007$). ⁸⁴
	No/possibly	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; conjunctival staining.	Nasal and temporal conjunctival staining was significantly higher for users of PHMB-containing systems ($P < 0.05$). No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, or burning or stinging; but grittiness or scratchiness was significantly higher with the PHMB-containing system. ⁷¹
Conjunctival indentation	Yes	A new method to measure contact lens osmolality was validated by testing for repeatability and by evaluating independence of lens material, power, and osmolality value of the lens. This method was then used in a clinical study. 15 subjects wore each of 9 different lens types. Osmolality, tear film, and ocular surface parameters were tested for their association with comfort using linear mixed model.	Comfort was associated with conjunctival indentation ($P = 0.002$, $r = -0.37$) (Stahl U, et al. <i>IOVS</i> 2009;50:ARVO E-Abstract 2611).
Palpebral conjunctival staining, including lid wiper staining and lid parallel conjunctival folds	Yes	Subjects were divided into 2 groups based on the presence or absence of dry eye symptoms. The lid wiper of asymptomatic ($n = 75$) and symptomatic ($n = 30$) soft contact lens wearers was examined following the instillation of fluorescein and rose bengal dyes. Lid wiper staining was graded zero to 3.	Eighty percent of the symptomatic subjects displayed lid wiper staining compared to 13% of the asymptomatic subjects ($P < 0.0001$). ⁹²

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
	Yes	Observational study; $n = 50$ (19 men, 31 women; mean age, 32.1 ± 11.4 y) adapted lens wearers. Comfort was evaluated using the Contact Lens Dry Eye Questionnaire. Corneal staining, lid wiper epitheliopathy, and lid parallel conjunctival folds were assessed in the right eyes. Nonparametric analyses were used to study differences between groups and correlations between objective tests and symptoms.	Lid wiper epitheliopathy and lid parallel conjunctival folds were significantly increased ($P < 0.035$) in the symptomatic lens wearers. ⁷²
Palpebral roughness	No/possibly	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; palpebral roughness.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging, but there was an increase in grittiness or scratchiness ($P = 0.045$) for the PHMB system and also an increased level of palpebral roughness ($P = 0.014$). ⁷¹
Conjunctival hyperemia	Yes	Cross-sectional study on 415 contact lens wearers in which a number of tear film, contact lens, and patient-related factors were measured and examined in relation to dry eye status. Univariate and multivariate logistic regression models were used, and data from 360 of the 415 subjects were used in the analyses.	Several factors were shown to be related to dry eye status in multivariate modeling, including limbal injection ($P = 0.03$). ⁷⁵
	No	Prospective, randomized, parallel-group, 3-mo study; $n = 120$ participants (40 in each group) wore 1 of 3 lens types (etafilcon A, narafilcon A, and senofilcon A), all worn bilaterally on a DD regimen. Participants were observed at baseline, 2-wk, and 1- and 3-mo visits in which ocular physiology and lens performance variables were collected on a 0–4 grading scale in 0.1 increments. Subjective comfort and vision ratings were collected on a 1–100 rating scale and in the form of symptom severity.	Even though 1 lens type was associated with significantly more limbal redness ($P < 0.01$), there were no differences in comfort between lenses ($P > 0.05$). ⁷²
Limbal hyperemia	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; limbal and bulbar hyperemia.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging (except grittiness or scratchiness), or for limbal or bulbar hyperemia. ⁷¹
Tear film stability	Yes	Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 h of lens wear, and differences in tear film characteristics between subject groups were determined. Tests were performed in absence of contact lens wear.	Tear stability (noninvasive tear breakup time) was significantly reduced in intolerant wearers ($P < 0.05$). ¹⁰⁷
	Yes	Cross-sectional study on 415 contact lens wearers in which a number of tear film, contact lens, and patient-related factors were measured and examined in relation to dry eye status. Univariate and multivariate logistic regression models were used, and data from 360 of the 415 subjects were used in the analyses.	Several factors were shown to be related to dry eye status in multivariate modeling, including rapid pre-lens tear film thinning time ($P = 0.008$). ⁷⁵

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
	Possibly	Randomized, double-masked, contralateral, 7-h nondispensing study; $n = 40$ (20 symptomatic and 20 asymptomatic lens wearers). Lens water content was measured before and after 7 h of lens wear, and pre-lens noninvasive tear film breakup time (NITBUT) was measured immediately after insertion and after 5 h of lens wear. Subjective comfort and dryness were rated at 0, 1, 3, 5, and 7 h of lens wear.	Symptomatic hydrogel contact lens wearers with decreased wearing time had measurably reduced NITBUT. ³⁵
	Possibly	Randomized, subject-masked bilateral crossover study of silicone hydrogel lenses in 24 adapted soft contact lens wearers.	Tear film stability was superior for 1 lens over the other, and the authors concluded that this was associated with an overall better comfort for this lens. ¹⁰⁵
	No	Prospective, 8-h nondispensing study; $n = 30$ adapted soft contact lens wearers (16 symptomatic and 14 asymptomatic) were fitted with etafilcon A lenses. In vivo wettability, NITBUT, and subjective symptoms (vision, comfort, and dryness) were assessed at baseline and after 2, 4, 6, and 8 h. After 2-, 4-, 6-, and 8-h time points, lenses were collected, and total protein, total lysozyme, and active lysozyme deposition were assessed.	There was no significant difference in the NITBUT values between the 2 groups at any time point ($P > 0.05$), but the 8-h time point was significantly lower than the baseline measurement in both the symptomatic and asymptomatic groups ($P = 0.032$). ¹⁰⁶
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; noninvasive and fluorescein breakup time.	No significant difference between 2 preservative system groups was noted for overall or end-of-day comfort, discomfort, burning or stinging (except grittiness or scratchiness) or for tear breakup times. ⁷¹
Tear film volume	Yes	Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 h of lens wear, and differences in tear film characteristics between subject groups were determined. Tests were conducted in absence of contact lens wear.	Tear volume (meniscus height and phenol red thread test) were significantly reduced in intolerant wearers ($P < 0.05$). ¹⁰⁷
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; tear meniscus height, Schirmer, and fluorescein clearance tests.	No significant difference noted between the 2 preservative system groups for overall or end-of-day comfort, discomfort, burning or stinging (except grittiness or scratchiness), and tear meniscus height, Schirmer test, or fluorescein clearance. ⁷¹
Tear lipid layer	Possibly	Randomized, subject-masked bilateral crossover study of silicone hydrogel lenses in 24 adapted soft contact lens wearers.	Lipid layer thickness was superior for 1 lens over the other, and the authors stated that this may have been a reason for the better comfort for that lens over the other. ¹⁰⁵
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; preocular tear film lipids.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging, except grittiness or scratchiness, and no difference in clinical assessment of tear film lipid layer. ⁷¹

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
Tear film osmolality	Yes	Cross-sectional study on 415 contact lens wearers in which a number of tear film, contact lens, and patient-related factors were measured and examined in relation to dry eye status. Univariate and multivariate logistic regression models were used, and data from 360 of the 415 subjects were used in the analyses.	Several factors were shown to be related to dry eye status in multivariate modeling, including increased tear film osmolality ($P = 0.05$). ⁷⁵
	No	Prospective, 8-h nondispensing, crossover study; the right eyes of 15 neophytes were included. Tear osmolality was measured before and after 4 and 8 h of each contact lens wear. Ocular comfort was assessed after 4 and 8 h of each contact lens wear.	Tear osmolality was not associated with ocular comfort. ¹¹⁴
	No	Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 h of lens wear, and differences in tear film characteristics between subject groups were determined.	Tear osmolality was not statistically significantly different between tolerant and intolerant contact lens wearers (osmolality [mOsmol/kg] 317.4 and 324.4, respectively, $P = 0.069$), even though intolerant wearers had a greater number of symptoms than tolerant wearers ($P < 0.05$). ¹⁰⁷
	No	A new method to measure contact lens osmolality was validated by testing for repeatability and by evaluating independence of lens material, power, and osmolality value of the lens. This method was then used in a clinical study. 15 subjects wore each of 9 different lens types. Osmolality, tear film, and ocular surface parameters were tested for their association with comfort using linear mixed model.	Comfort after 6 h of lens wear was not associated with tear osmolality after lens wear ($P = 0.993$). ⁸⁵
Contact lens osmolality	Yes	A new method to measure contact lens osmolality was validated by testing for repeatability and by evaluating independence of lens material, power, and osmolality value of the lens. This method was then used in a clinical study. 15 subjects wore each of 9 different lens types. Osmolality, tear film, and ocular surface parameters were tested for their association with comfort using linear mixed model.	Comfort after 6 h of lens wear was associated with the osmolality of the worn lens ($P = 0.006$, $r = -0.41$). Osmolality of worn lenses significantly correlated with tear film breakup time ($P = 0.003$, $r = -0.22$), lens water content ($P < 0.001$, $r = -0.58$), conjunctival indentation ($P < 0.001$, $r = 0.45$), and ocular sensitivity ($P < 0.05$) after 6-h lens wear. ⁸⁵
Optical quality	No peer reviewed publications on this topic		
Corneal sensitivity	Yes	$N = 32$ symptomatic and 29 asymptomatic contact lens wearers (aged 20–42 y, 6 males and 26 females; and 21–36 y, 9 males and 20 females, respectively). Mechanical stimulus thresholds of the cornea were determined using a Belmonte pneumatic esthesiometer and the ascending method of limits. Then 3 stimulus intensity groups (subthreshold, threshold, and suprathreshold) were applied to the eye in random order, each 20 times. Subjects rated the intensity of the stimuli using a scale of zero to 4. The rating data from the 2 groups were compared by Friedman nonparametric ANOVA. Adaptation was defined as the reduction in subsequent ratings compared with earlier ones.	Adaptation was found to suprathreshold mechanical stimuli in the asymptomatic group but not in the symptomatic group ¹²¹ ; in other words, the symptomatic group responded as much to the first suprathreshold stimulus as the last and never gained “tolerance” to the stimulus. ¹²¹
	No	Non-contact lens wearers and subjects who had worn soft contact lenses for more than 1 y were recruited and were divided into 3 groups: (1) normal controls, (2) contact lens wearers without dry eye, (3) contact lens wearers with dry eye. Corneal sensitivity was measured with a Cochet-Bonnet esthesiometer. Nerve density and branching in the subepithelial plexus were measured using in vivo confocal microscopy. Tear nerve growth factor and tissue growth factor-beta1 levels were measured with an enzyme immunoassay.	Both sets of contact lens wearers had reduced corneal sensitivity ($P = 0.032$) compared to the normal controls, ¹²² but there was no difference in sensitivity between contact lens wearers with and without dry eye complaints.

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
Conjunctival sensitivity	Yes	Fifteen subjects, 9 lens types, lenses worn for 6 h; sensitivity measured with an air jet aesthesiometer at baseline and following lens removal.	Comfort associated with a change in corneal and conjunctival sensitivity. ¹⁵⁹
In vivo contact lens wettability	No	Prospective, randomized, bilateral, crossover study; $n = 15$. Initial comfort and surface wettability were compared between 3 lens types (Novalens [Ocu-Tec, Bellshill, North Lanarkshire, UK], ENVISION [Bausch & Lomb], and D3X4 [Wesley-Jessen, Des Plaines, IL]).	Initial comfort was significantly better with the D3X4 lens; no significant difference was found between the 2 rigid lens materials. No significant difference in lens surface wettability was found between the 3 materials. ¹²⁴
	No	Prospective, 8-h nondispensing study; $n = 30$ adapted soft contact lens wearers (16 symptomatic and 14 asymptomatic) were fitted with etafilcon A lenses. In vivo wettability, NITBUT, and subjective symptoms (vision, comfort, and dryness) were assessed at baseline and after 2, 4, 6, and 8 h. After 2-, 4-, 6-, and 8-h time points, lenses were collected, and total protein, total lysozyme, and active lysozyme deposition were assessed.	In vivo wettability was reduced over the course of the day for both groups, but was not statistically significant ($P > 0.05$). There was also no significant difference in wettability between the 2 groups at any time point ($P > 0.05$). ¹⁰⁶
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness, and visual changes; noninvasive and fluorescein breakup time; preocular tear film lipids, tear meniscus height, Schirmer, and fluorescein clearance tests; limbal and bulbar hyperemia; palpebral roughness; corneal and conjunctival staining; lens front surface wetting; and lens film deposits.	Front surface lens wettability was significantly better for group IV polyquaternium-1 users compared to PHMB users ($P = 0.008$), with 84% vs. 72%, respectively, with lenses graded by the investigator as having "good" or "excellent" wettability. No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging, grittiness or scratchiness. ⁷¹
Ex vivo wettability	Possibly	Randomized, single-masked study, $n = 6$; test and control lenses were soaked for 12 h in either saline or 1% aqueous solution of poloxamine 1107. The advancing and receding contact angles were determined ex vivo after various periods of wear.	Control saline-soaked lenses exhibited no change in wetting angles over time, indicating a lack of surface modification by components within the tear film. Poloxamine-soaked lenses exhibited a significantly reduced advancing angle ($P < 0.001$) and hysteresis angle ($P < 0.001$) when compared with control lenses. In addition, treated lenses were consistently rated as more comfortable than control lenses ($P = 0.04$). ¹²⁵

eyelid margin has also been identified.⁹³ The suspected etiology of this epitheliopathy is increased friction between the lid wiper area and the surface of the cornea or contact lens as a result of inadequate lubrication⁹⁴; however, this etiology still needs to be tested.

There are studies suggesting that LWL is more frequent in individuals reporting CLD; however, there have been no studies showing that the amount of LWL is related to the level of symptoms. Confirmatory studies are necessary to determine whether LWL is a good outcome measure of CLD. Standardization of dye instillation and assessment are also warranted since various methodologies have been reported.^{92,95} There is one study that showed a possible effect of palpebral roughness on the symptoms of grittiness and scratchiness during contact lens wear.⁷¹

Lid Parallel Conjunctival Folds. Lid parallel conjunctival folds (LIPCOF) have been described by Hoh et al.⁹⁶ and are defined as subclinical folds parallel to the upper and/or lower eyelid margin in the temporal and nasal areas of the bulbar conjunctiva. Lid parallel conjunctival folds have been shown to be significantly increased in symptomatic contact lens wear-

ers⁹⁶⁻⁹⁸ and to be positively correlated with LWL.⁹⁷ While LIPCOF may be predictive of CLD, prospective studies to investigate onset and recovery and whether the severity of LIPCOF is related to the severity of CLD are warranted.

Conjunctival and Limbal Hyperemia. Vascular dilatation can occur with CL wear.^{67,75} Conjunctival hyperemia is often increased with contact lens wear compared to non-lens-wearing eyes.^{99,100} However, since conjunctival hyperemia is affected by a number of factors, such as corneal hypoxia,¹⁰¹ protein adsorption with lens overwear,¹⁰² and lens fit,¹⁰³ it has generally not been a good outcome measure or predictor of CLD.

Tear Film Stability. Changes in tear film stability occur with CL wear.^{35,71,75,104-106} There have been mixed reports about the relationship between tear film stability and contact lens comfort. Reduced tear film stability has been reported in symptomatic and intolerant contact lens wearers,^{75,107} while Fonn et al.,³⁵ Guillon and Maissa,³⁶ and Guillon et al.¹⁰⁸ report no difference in tear stability between symptomatic and asymptomatic contact lens wearers in the absence of lens wear. Various techniques are used to assess tear film stability,

and it has been noted that endpoint criterion used for measurements can also differ.^{109,110} Standardization in methodology would be helpful to further evaluate the relationship between tear film stability and CLD. No optimal method for assessing tear film stability has yet been defined or validated, and this is needed.

Tear Volume. Tear volume can vary with CL wear.^{71,104} Tear volume has been measured noninvasively by measuring tear meniscus height, which has been done with use of a slit lamp and grading system or with more sensitive measurement techniques, such as optical coherence tomography (OCT). Tear meniscus height as measured by OCT has been reported to contribute to ocular comfort in both symptomatic and asymptomatic wearers.¹⁹ Glasson et al.¹⁰⁷ have shown that tear meniscus height (and area) is different between tolerant and intolerant lens wearers and that contact lens intolerance was best predicted by a combination of clinical variables, including tear film stability, tear volume, and the number of symptoms reported.

Tear Film Lipid Layer. The tear film lipid layer is affected by CL wear.^{71,105} The lipid layer is generally graded on a scale that uses interference patterns to estimate the thickness of the layer.^{108,111} The thickness of the lipid layer has been correlated with the evaporation rate of the tear film.¹¹² As contact lens wear increases the evaporation of the tear film,¹¹³ it has been assumed that there may be a relation between lipid layer thickness and CLD. Nichols and Sinnott⁷⁵ showed in a sample of 360 lens wearers that reduced lipid layer thickness was predictive of contact lens dry eye, in addition to being correlated with an increase in pre-lens tear thinning (a surrogate for evaporation). However, that relationship, if one exists, has not been conclusively shown.

Tear Film Osmolarity. Osmolarity of the tear film is a sensitive marker of tear function.^{75,104,107,114} (Stahl U, et al. *IOVS* 2009;50:ARVO E-Abstract 2611). Tear osmolarity has been shown to change with contact lens wear¹¹⁵; however, there have been mixed results as to whether it can be used to predict CLD. It has been recommended that for bilateral measurements, the more severe measurement be analyzed due to the asymmetric effects of environmental stress.^{115,116} With respect to methodology, it should be indicated whether measurements were completed with the lens on the eye or after it had been removed, since removal may result in reflex tearing and may result in lower values.⁷⁵

While tear film osmolarity has been related to symptoms of dry eye in non-contact lens wearers, its effect on CLD is less clear. However, contact lens osmolarity (i.e., a property of the contact lens itself) has been associated with CLD⁸⁵ (Stahl U, et al. *IOVS* 2009;50:ARVO E-Abstract 2611), and additional studies would be helpful to better understand this potential outcome measure.

Optical Quality. Papas et al. (Papas E, et al. *IOVS* 2003;44:ARVO E-Abstract 3694) suggest that poor optical quality may have a psychological impact on perceived ocular comfort and it may be that lens awareness as a result of reduced optical quality is related to CLD. With contact lens wear, reduced optical quality can be related to a number of factors, including uncorrected refractive error, higher-order aberrations,^{117,118} and poor front surface lens wettability.^{119,120} Currently, there is insufficient information to make conclusions regarding the link between optical quality and CLD; therefore additional research is warranted. Challenges will likely include methods of testing, since subtle vision changes are not adequately measured using traditional visual acuity measures. The development of dynamic vision assessments, taking into account environmental factors and blink patterns, may be warranted.

Ocular Sensitivity. Ocular sensation may be altered by CL wear.^{85,121,122} Trials measuring corneal sensitivity in contact lens wearers have used either the Belmonte pneumatic esthesiometer or the Cochet-Bonnet esthesiometer, and it would be expected that results could be impacted by the measurement technique. Overall, there have been few clinical trials investigating this outcome. Conjunctival hyperesthesia has been reported in dry eye subjects¹²³ but has not been explored in subjects with CLD.

Contact Lens Surface. The surface of the contact lens is a critical interface.^{71,106,109,124,125} The relationship between contact lens wettability and CLD has been unclear, possibly related to the various techniques that are used to assess wettability in vitro and in vivo and their limitations in capturing the dynamic changes that occur with wear and between blinks (for more in-depth analysis see the report of the Contact Lens Materials, Design & Care Subcommittee). Validation of measurement and grading techniques and a better understanding of the variability of in vivo wettability may be beneficial in determining the role that wettability plays in CLD.

Contact Lens Deposition. A correlation has been reported between active lysozyme on worn lenses and subjective comfort ($r = 0.6-0.7$; $P < 0.001$).¹⁰⁶ Additionally, a study of mucin mobility on worn contact lenses has been conducted, and changes in MUC1 breakdown were significantly negatively correlated to the overall Ocular Surface Disease Index score ($r = -0.891$, $P = 0.001$).⁷² However, the overall concentration of protein or cholesterol that can be extracted from contact lenses was weakly if at all correlated to comfort during lens wear (as measured on a VAS).¹²⁶ Additional studies investigating the role of contact lens deposition and CLD are necessary.

A number of studies have measured CLD and clinical signs with contact lens wear but did not determine whether there was a relationship between signs and symptoms.^{15,17,21,23,31,32,38,127-135} This complicates the interpretation of outcomes related to CLD since the specific driver(s) of CLD cannot be determined. In addition, when correlations have been measured, often there is not a test for a direct causative effect. A number of studies have reported changes in clinical outcomes with contact lens wear; however, there has been little evidence or discussion as to whether these findings are clinically relevant.

Studies With the Primary Objective of Predicting CLD. There have been only a few studies with this primary objective. Berry et al.⁷² evaluated signs and symptoms (using the CLDEQ) in 19 men and 31 women (mean age 32.1 ± 11.4 years) and reported that symptomatic contact lens wearers exhibit significantly more LWE and LIPCOF and decreased MUC5AC reactivity. Using a similar study design, Pult et al.⁹⁷ also reported that contact lens wearers with dryness symptoms exhibit significantly more LWE and LIPCOF, but not increased corneal staining, bulbar hyperemia, or decreased pre-lens tear breakup time. In a prospective, 2-month longitudinal study, Michel et al.¹³⁴ investigated new contact lens wearers and grouped them according to their response to the screening CLDEQ questions, resulting in 20 "symptomatic" and 13 "asymptomatic" subjects. They reported that the best combination to predict CLD using logistic regression was LIPCOF sum plus noninvasive tear breakup time (NITBUT) and OSDI scores (positive predictive value, 87%; accuracy, 91%).¹³⁴ Nichols and Sinnott⁷⁵ evaluated data from 360 contact lens wearers (33/360 were gas-permeable lens wearers) from a large cross-sectional study and reported several factors to be related to dry eye status in multivariate modeling, including female sex ($P = 0.007$), lenses with higher nominal water content ($P = 0.002$), rapid pre-lens tear film thinning time ($P = 0.008$), frequent usage of over-the-counter pain medication (P

= 0.02), limbal injection ($P = 0.03$), and increased tear film osmolality ($P = 0.05$). In a prospective, observational multicenter study conducted by Young et al.,¹³⁵ symptomatic soft contact lens wearers reported significant soft contact lens-related dryness using the CLDEQ preceding a protocol-driven dry eye examination. Of the 226 symptomatic wearers examined, 23% were without signs. The wearers classified as “No dry eye signs” had significantly longer prelens breakup time (9.8 vs. 6.6 seconds, $P < 0.0001$), better lens wetting (3.4 vs. 2.4 [0–4 scale], $P < 0.0001$), and lower levels of film deposits on lenses (0.45 vs. 0.92 [0–4 scale], $P < 0.0001$), and most slit-lamp signs. The wearers with no signs of dry eye were significantly more likely to be male (36% vs. 19%, $P = 0.013$), were less likely to have deteriorating comfort during the day (81% vs. 97%, $P = 0.001$), reported longer average hours of comfortable wear (11 ± 3 vs. 9 ± 4 hours, $P = 0.014$), had older contact lenses (18 ± 14 vs. 13 ± 12 days, $P = 0.029$), and had greater intensity of photophobia early and late in the day ($P = 0.043$ and 0.021).¹³⁵ Glasson et al.¹⁰⁷ demonstrated that the type of drying of the tear film (spot versus streak during the interblink period), the number of ocular symptoms in absence of lens wear, and the tear meniscus area best differentiated tolerant from intolerant lens wearers.

The combined results of these studies suggest that the clinical outcome variables of tear stability, tear meniscus height/area, LWE, and LIPCOF are most likely to be predictive of CLD, although predictive factors have yet to be evaluated prior to wear to be able to identify wearers likely to get CLD. However, LWE and LIPCOF may only allow classification of participants in trials into symptomatic and asymptomatic groups and may not be able to predict other aspects such as the increase in symptoms over the course of 1 day of contact lens wear. It would be beneficial if additional testing were completed to determine whether these are good outcome measures of CLD. An ideal outcome measure is one that is a good predictor of the level of CLD and one that is also modifiable in order to confirm the relationship with CLD and to evaluate treatments. Provocative testing may be a strategy to better understand the impact of contact lens wear on clinical measures and to control for confounding factors.

As mentioned previously, many of the clinical trials investigating CLD have focused on the symptoms, but little attention has been given to the visual aspect of CLD. Yang et al.¹¹ investigated the effect of lens care systems on blink rate, ocular discomfort, and visual performance, but did not determine whether there was a relationship between these variables.

Conclusions Regarding Outcome Measures

A goal of future studies should be to establish needed standardization and agreement for the outcome measures related to CLD. An ideal outcome measure would be objective, internally and externally valid, and measurable with minimal bias. To better understand the predictors of CLD, it is recommended that more fundamental, basic clinical trials be conducted in order to at least understand which outcome variables are related to CLD and what level of change is clinically meaningful. Once our understanding of these basic questions is improved, more advanced study designs can be employed to comprehensively evaluate in-eye performance of existing and emerging technologies. A few key considerations for future outcome measures related to CLD are understanding of onset and recovery; cause or effect relationship with symptoms; knowledge of clinically meaningful changes; identification of confounding factors; consideration of timing, so that outcome measures and symptoms are assessed at

similar time points; validation of testing methodology; standardization of grading scales, as well as observation techniques.

Considerations for Clinical Trial Design

Design and performance of clinical trials should follow the guidelines of good clinical practice, which are extensively reviewed in the 2007 Report of the International Dry Eye Workshop and are not repeated herein.¹³⁶ A simple checklist for conduct and reporting of a clinical trial is the CONSORT recommendation (in the public domain at www.consort-statement.org).¹³⁷ Understanding CLD requires careful thought and consideration when it comes to the design of a study. Many factors can have adverse impact upon the variables being measured and thus the results.

The possible interrelationship between lens comfort and many other variables such as lens wearing time, lens care system used, lens material, lens design, form of vision correction (i.e., single vision, toric, or multifocal), current ocular disease, general health of the study participant, or use of medication requires that all these features be carefully controlled and considered. Many other factors about the study participant or the observer may inadvertently introduce bias and again must be considered with regard to the study design.

Trial Design. Consideration must be given to the correct clinical trial design. Prospective design with appropriate randomization of subjects is key. Clinical trials may employ single-eye, fellow (contralateral)-eye,¹³⁸ or crossover designs,^{15,139} but there are advantages and limitations to each trial design depending upon the question being asked and the length and level of supervision of the trial. In any case, avoiding bias is an important consideration when designing a clinical trial, and studies comparing lens comfort performance by collecting data from right and left eyes should consider having participants wear the test lens and control in both eyes. When these methods are used, it is important to consider whether discomfort in one eye can influence assessment made in the other or whether the study participant has a preference toward one eye. When this preference is demonstrated to be strong, the lens wearer should be considered ineligible for the study. To avoid such bias, test and control lenses may have to be crossed over and worn bilaterally, and then comfort assessment would be the mean for each eye.

Appropriate Data Collection. Frequently lens comfort studies collect data that is subjective or opinion based. The tool used to collect these data must be carefully evaluated and crafted, whether the study is using a VAS, a numerical rating scale, a Likert scale, or a questionnaire. Visual analogue scale data may lack sensitivity, as most data points may be skewed toward one end of the scale or artificially enhance sensitivity by scale expansion.¹⁴⁰ The impact of ceiling and floor effects must also be evaluated. Some validated questionnaires thought to be useful in assessing lens comfort may also lack sensitivity due to the different populations that may have been used as part of their validation.¹⁴¹ A specific questionnaire oriented toward lens comfort would be needed. Another consideration is that reported lens comfort changes both over the day of wear and over the life of the lens,^{34,35} making the collection of these data time sensitive. Different methods have been trialed to ensure that data of this type are recorded by the study participant in a timely way. Stone et al.¹⁴² used paper diaries that electronically recorded when data entries were made and found that 90% of the study participants hoarded time-sensitive data to one entry time point, encouraging the conclusion that paper-based diaries were not ideal. The incorporation of electronic devices to collect data directly has also been tried

in various clinical trials with variable levels of compliance pertaining to recording time-sensitive data.^{143,144} Relating to the field of contact lenses, Morgan et al.¹⁴⁵ reported high levels of compliance, with 93% of study participants responding within 30 minutes when requested via SMS messaging; Plowright et al.¹⁴⁶ reported between 76% and 82% responding, but the time delay for the response to their SMS messages was not reported. Woods et al.¹⁴⁷ developed an online Web-based system allowing entry via smartphones and reported a response rate of 97.5%, with 84.1% responding within the allotted time window for time-specific data. The use of smartphones with a data collection method for time-sensitive data would appear to be an obvious recommendation, particularly as their use is now considered to be ubiquitous.¹⁴⁸

Clearly Written Protocols. The process for conducting the study must be clear, and the protocol must describe each step of the study design as well as methods of data collection. It has been reported that CLD is time dependent, in relation to both length of lens wear and diurnal variation, and those features should be considered when one is measuring or differentiating lens comfort.³⁴

Inclusion of Appropriate Controls. Consideration must be given to ensuring that the correct control is used, in addition to the inclusion of an arm in which no change in products is made. Confounding influences must be considered. For a study that is investigating the impact of lens material on comfort, the lens care system being used must be carefully controlled. Studies have reported that different lens materials in combination with lens care systems can influence lens comfort.^{11,139}

Adequate Length of Trial. The length of time a contact lens has been worn (both during 1 day and over the recommended life of the lens in days) has been shown to affect lens comfort.^{34,35} Therefore, comparisons to be made between studies to record end-of-day comfort must be associated with how long the lens has been worn in elapsed hours. The age of the lens also influences discomfort and should be recorded.³⁴

Run-In and Washout Periods. In order to compare the performance of a contact lens, all study participants should be exposed to the same conditions before the study starts as well as during periods between various phases of the study. During a run-in period at the start of a study, the participant's method of vision correction should be consistent, that is, a period of spectacle wear or all participants wearing the same lens type with a consistent lens care system. The same provision is advised for periods between study phases.

Adequate Sample Size. Sample size calculations should be considered before the study begins, except in the case of pilot studies that are intended to generate data from which sample size can be calculated. For determination of sample size it is important to consider the variability of the primary variable being measured and a clinically meaningful difference in the variable.

Prevention of Disclosure of Masking. Frequently, lenses used in studies have engravings or markings on them rendering difficult, if not impossible, any attempt to mask the study participant with regard to the lens being used.¹⁴⁹ Having a research assistant insert and remove the lenses may avoid the study participant's identifying the lens but may not be practical for all study designs. The researcher observing and recording physiological changes should do so with the lens removed by another researcher to maintain the masking. The researcher who assesses lens fit should not collect other data in the study.

Evaluation of Effectiveness of a Treatment/Modification. This type of evaluation is used to assess whether a specific treatment or modification aimed at improving CLD has had an effect. In addition to a better score on the subjective

rating scale used, increased wearing time, increased comfortable wearing time, reduction in the frequency or intensity of symptoms, preference ratings, and quality of life information may all be potential ways of assessing the effectiveness of such a treatment.

Questionnaire Length. When designing a questionnaire, it is important to consider participant fatigue. If the questionnaire is too long, this may encourage bias—habit bias or self-limiting bias (see below). Use of validated questionnaires is advisable.

Collection of Data. When designing a clinical study it is important to consider what the key variables are and not to try to collect every variable possible. This can make the study visits burdensome and induce fatigue, increasing variability. Some variables may affect others, that is, have an order effect. Use of fluorescein to assess corneal staining will affect a subsequent assessment of NITBUT. Repeated NITBUT assessments may affect a subsequent measure of vision.

Appropriate Statistical Analysis. Parametric statistical tests should not be used on data that are not normally distributed or continuous in nature. Careful consideration should be given to the appropriate statistical tests, and this should be described in the study protocol.

Generalizations Outside of Study Results. Reports or discussion in papers should expand only on the results from the study. It is important to remember that the study results relate only to the population tested and that the study population is not likely to be representative of all populations; avoid cohort bias.

Discussion of Potential Bias. Collecting subjective data can lead to various types of bias. Bias can be very difficult to control, so potential types of bias should be evaluated¹⁴⁹ (see later sections on bias).

Evidence- versus opinion-based conclusions: Careful consideration needs to be given to the pyramid of evidence. Randomized clinical trials (RCTs) provide significantly stronger evidence than anecdotal opinions from experts or the authors. Care should be taken to ensure that reporting focuses on factual evidence.

Excessive Reuse of Study Subjects. Subjects who are regularly used by a research center as study participants can effectively become trained observers. If not taken into account, this could lead to bias and skew the study results. When conducting research it is important to monitor the frequency with which study participants are enrolled. Creating a pool of trained participants can be advantageous for a particular investigation. Consideration should be given to reporting the frequency with which study participants have been used in similar study designs.

Ethics/Institutional Review Boards/ClinicalTrials.gov Registration. The data collected from a study are of greater value when the study has been conducted as a RTC. The guidelines of good clinical practice (in the public domain at <http://ichgcp.net>) should be employed. Prior ethical review and approval are mandatory, and registration of the clinical trial is desirable and is becoming mandatory.

Disclosure of Conflicts of Interest. Researchers and authors need to pay careful attention to potential conflicts of interest, and these must be declared.

Study designs that can be used to report on CLD at different phases of development are outlined in Table 4.

AVOIDING BIAS AND ENSURING QUALITY IN CLINICAL TRIAL DESIGN AND PERFORMANCE

There are many sources of potential bias in conducting a clinical trial. If not recognized, the bias can invalidate

Investigative Ophthalmology & Visual Science

TABLE 4. Candidate Designs for Clinical Trials

Design Criteria	Study Phase			
	Lens Design Phase 1	Biocompatibility Phase 2	Dispensing Phase 3	Postmarket Phase 4
Main purpose	Emphasize short-term on-eye performance and comfort, for example, assessment of effects of lens edge, case curve, thickness, optic zone	Emphasize the effect of material/tear film interactions on comfort and vision (variability). Examine the effects of changes to materials, surfaces, packaging solutions.	Measure "normal use" performance over lens life. Emphasize material/tear film interactions on comfort and vision (variability). Measure adverse events during lens wear. Assess effects of changes to material, lens care, lens/surface aging.	Measure use after lenses released for sale. Examine the wearer's experience. Assessment of adverse events during lens wear.
Features	Short-term (minutes to hours) Direct supervision Many sequential comparisons acceptable Account for order effect Contralateral design may be acceptable, but not if this stimulates excess tearing in one eye Questionnaire design—enhance differences Double masking Ensure adequate control/tests for potential false-positive results. That is, if changing from lens A to B and assessing comfort, also include masked change from lens A to lens A.	Short- to mid-term (4–12 h) Direct supervision Not often sequential Could assess effects of packaging solution vs. being cycled in lens care Contralateral design may be acceptable but not if it stimulates excess tearing Questionnaire design -Diurnal changes -Recall period Double masking Pre- and postexposure testing of ocular surface staining	Mid- to long-term (days to months) In-home use/dispensing Lens care assigned if using reusable contact lenses Crossover preferred to contralateral design Need to define washout period Questionnaire design -Diurnal changes -Recall period Observer masking more critical; wearer masking if possible Pre- and postexposure testing of ocular surface staining	Cross section Prospective cohort Registry
Essentials	Double masking Ensure adequate control/tests for potential false-positive results. That is, if changing from lens A to B and assessing comfort, also include masked change from lens A to lens A.	Double masking Pre- and postexposure testing of ocular surface staining	Observer masking more critical; wearer masking if possible Pre- and postexposure testing of ocular surface staining	Breadth Variety of clinical settings
Population	Can be asymptomatic wearers to determine whether change is detectable Could select difficult-to-fit subpopulation Understand habitual symptom state	Possible participant groups include poor "wetters," symptoms vs. no symptoms Must be able to attend visits after lens fitting On premises best for new materials in case of need for emergency lens removal Determine clinically meaningful and statistically significant differences Clinic	Possible participant groups include poor "wetters," symptoms or no symptoms Account for adverse events between scheduled visits	Fewer exclusion/inclusion criteria
Outcomes	Decide on meaningful differences with scales Clinic	Determine clinically meaningful and statistically significant differences Clinic	Determine clinically meaningful and statistically significant differences Home use	Determine clinically meaningful and statistically significant differences Home use Remote access
Setting	Clinic	Clinic	Home use	Home use Remote access

conclusions and, even if recognized before data analysis, may not be amenable to compensation in the final analysis. Therefore it is worthwhile to identify and avoid such bias. Bias can be introduced at several junctures in a clinical trial. Bias can be grouped into several categories.¹⁵⁰ These include selection bias, performance bias, detection bias, attrition bias, reporting bias, psychometric bias, and statistical bias.

Selection Bias

This generally concerns a lack of comparability of baseline characteristics between intervention groups. This can be due to lack of random sequence generation to produce comparable groups or due to inadequate allocation concealment—concealment that is insufficient to mask study investigators to forthcoming treatment assignments and could thus result in nonrandom allocation of subjects. One of the most frequent sources of selection bias occurs with entry criteria that fail to segregate a study population into appropriate trial groups. As one example, if a diagnostic test is being validated against other tests and the first diagnostic test is included in the selection process for identifying subjects to be tested, there is a high probability that such a test will perform better than other tests due to the criterion of selection. This bias is occasionally encountered in evaluation of dry eye disease in which multiple contributory factors are responsible for the expression and severity of disease but are not appropriately compared. One way to attempt to avoid such bias is to use a composite (and possibly weighted) index to establish presence of disease.

Another form of selection bias is *spectrum bias*, in which study subjects may be selected from only a portion of the entire spectrum of disease severity. This bias would weigh heavily against an evaluative test that had accuracy over the entire spectrum of disease but not with as great a differential performance as a second test that identified a more limited subset of disease. This bias can be avoided by ensuring that the entire spectrum of a disorder is included in the test population if results are to be generalized to a larger population. It is also necessary to include a large enough population that the entire spectrum of disease is captured.

External validity can be questioned when the study population is not representative of the whole, which is more likely to occur with small sample sizes. One should not assume that the answers to a given survey match those for the whole population if the sample is small. Too many studies have small sample size as noted in the prior summary of published clinical trials.

Performance Bias

This can occur due to inadequate masking of subjects or investigators. Knowledge of the allocated interventions on the part of participants and personnel during the trial may lead to differential provision of care to participants in one group as compared to the other. Inadequacy of masking does not need to be prior to allocation in order to bias results. If subjects or investigators are able to determine which treatment they are on at any point in the trial, this can cause bias (e.g., the patients' reporting of symptoms, as well as the investigators' interpretation of test findings, which in this case is also somewhat subjective—that is, the investigator “grades” some parameter).

Detection Bias

This is due to inadequate masking of outcome assessment for the participants and investigators and subsequent systematic differences in the assessment of study outcomes between randomized intervention groups.

Attrition Bias

This is due to systematic differences between groups in outcome data either in the amount, nature, or handling of incomplete data or to violations of study protocol.

Reporting Bias

This can occur when reporting of outcomes is selective. A type of reporting bias occurs when there are systematic differences between reported and unreported findings (e.g., pulling out and preferentially reporting only statistically significant findings and not reporting those that were analyzed but found not to be statistically significant). This can be referred to as outcome bias or selective reporting bias.

Psychometric Bias

This bias depends upon the responsiveness of the subject and thus is less easily detected and recognized but may be a particularly obstructive effect in the analysis of subjective tests. *Habit bias* occurs when responders stop thinking and answer “Yes,” as all previous answers have been “Yes.” This may be due to fatigue or may occur when the survey is too long or too complex. Habit bias can result in misclassification that will either reduce study power if nondifferential among randomized groups, or may bias study findings if differential among randomized groups.

The Hawthorne effect occurs when respondents respond differently simply because they are being asked the question. This effect tends toward a positive bias: Subjects give the answer they think the investigator wants. This is similar to the bias that occurs simply due to testing a different lens on the eye. For example, subjects might rate a new lens type/design given to them as more comfortable than their previous lens simply because it is new. To minimize this bias, subjects should be randomized to receive a new lens type/design, masked if possible, and also a new lens that is simply a fresh lens of their previous type/design. In other words, in interventional clinical trials, placebo and nocebo effects must be considered. A placebo has been defined as “a substance or procedure . . . that is objectively without specific activity for the condition being treated,” and a “placebo effect” often occurs when the subject has a strong desire for the intervention in question to be successful.¹⁵¹ The opposite effect is seen when a subject who disbelieves in a treatment experiences a worsening of symptoms. This is called a nocebo effect.¹⁵²

Self-Limiting Bias

Self-limiting bias occurs when respondents try to make themselves appear in a positive light: Subjects give the answer they think makes them right. *Recall bias*, in which the participant may get things wrong, has several potential causes, such that the question being asked to collect factual data should not be too complex or rely on extensive memory recall.¹⁵³ The method of asking contact lens wearers what they are wearing (by asking them from memory, or showing a photograph of lens packaging or showing the actual packaging), particularly with respect to the name (brand) of lens and lens care system or manufacturer of products, can result in recall bias.

Statistical Bias

This occurs in several forms. For a clinical trial, internal validity, the extent to which systematic error is minimized, requires control of selection bias (biased allocation to comparison

groups), performance bias (unequal provision of care apart from treatment under evaluation), detection bias (biased assessment of outcome), and attrition bias (biased occurrence and handling of deviations from protocol and loss to follow-up). External validity (the extent to which results of trials provide a correct basis for generalization to other circumstances) requires control of patients' age, sex, severity of disease and risk factors, comorbidity, or the treatment regimen's dosage, timing and route of administration, type of treatment within a class of treatments (concomitant treatments), settings (level of care [primary to tertiary] and experience and specialization of care provider), and modalities of outcomes (type or definition of outcomes and duration of follow-up).¹⁵⁴

A particularly problematic data analysis effect is Simpson's paradox (Yule-Simpson effect).^{155,156} This occurs when a trend that appears in different subgroups of data is not seen when these groups are combined and indeed the reverse trend is demonstrated for the aggregate data. An example of this effect is the sex bias case at a major university alleging bias against women who had applied for admission to graduate schools there. The admission figures showed that men applying were more likely than women to be admitted, and the difference was so large that it was unlikely to be due to chance.^{157,158} In the total cohort there were 8442 male applicants, 44% of whom were admitted to jobs, and 4321 female applicants, 35% of whom were admitted to jobs. But when examining the individual departments, it appeared that no department was significantly biased against women. In fact, most departments had a small but statistically significant bias in favor of women.¹⁵⁸ The research paper by Bickel et al.¹⁵⁷ concluded that women tended to apply to competitive departments with low rates of admission even among qualified applicants (such as the English department), whereas men tended to apply to less competitive departments with high rates of admission among the qualified applicants (such as engineering and chemistry). Alternative impersonal terms for Simpson's paradox are reversal paradox and amalgamation paradox.

An additional feature of data analysis that can occur if a limited number of measurements of outcome values are obtained is regression to the mean. This is the phenomenon in which a variable is extreme on its first measurement but will tend to be closer to the average of its range on subsequent measurements.¹⁵⁸

There are other possible sources of bias, many of which pertain only to particular study designs (e.g., carryover in crossover trials and recruitment bias in cluster randomized trials). At other times, less common types of bias may arise under specific circumstances in a trial (e.g., contamination of intervention groups, whereby the experimental and control interventions get mixed, for example, if participants switch their lens care systems or contact lenses).

Recognizing that there are many potential bias effects in design and conduct of clinical trials is important to help avoid them or correct for them in data analysis.

RECOMMENDATIONS

General recommendations for design of clinical trials that categorizes study by lens design and duration of trials have been summarized in Table 4. The best design is a prospective, randomized, double-masked clinical trial. The question whether these designs should incorporate parallel-group, contralateral-eye, or crossover design as the most appropriate depends upon the specific question being investigated in the trial. Contralateral and crossover trials help to control for variations in subject psychological pain tolerance, but suffer the disadvantage of having the potential of development of

tolerance to any given stimulus in the same subject during the duration of the study. It is also possible that a sensation of pain or discomfort in one eye may have an impact on the reporting of pain or discomfort in the fellow eye.

Regardless of the design, appropriate entry criteria and adequate sample size are critical. Also, appropriate masking of both subject and investigator is critical. In contact lens-related trials, masking can be complicated by the type of lens being evaluated, the cleaning and lubrication solutions employed, and the wearing schedule. Inherent lens characteristics (e.g., markings, tint, and shape) may prohibit true masking of investigators in some instances. Finally, based upon our review of the literature, no specific clinical outcome instrument can be recommended, but the CLDEQ-8 most approaches the best validated device. It is clear that there needs to be more work on developing specific and efficient questionnaires for contact lenses—that they should be specific, that is, for soft, gas-permeable, or scleral lenses—rather than assuming that one questionnaire will work for all. The use of technology that allows easy data entry and time tracking (e.g., smartphone, call-in, online ratings, or other time capture methods) is recommended.

Modern experimental design is generally in two forms—one with fixed characteristics (primarily duration/sample size) and the other with adaptive characteristics (in which critical aspects [e.g., sample size and duration] are defined, a priori, as being modifiable). Under the current circumstances, the most appropriate design would be the former.

What variables will be important to manipulate in order to demonstrate lens-related discomfort effects, inclusion of control/placebo groups, determination of the duration of the experiments and how frequently the intervals will be sampled, what hypotheses are being tested, and what statistical tests to perform are important considerations. Until these at least are tied down, there is no rational way to design experiments. It is also possible that many nontrial experiments need to be done. The lack of an evidence base for many outcomes and predictors might necessitate that pilot validation experiments be conducted before any trial is designed. Finally, the epidemiology of the outcome itself is poorly understood, so it is possible that basic prevalence data are required, as well as population-based long-term incidence studies, before any interventional experiments are designed.

SUMMARY CONCLUSIONS

Prior clinical trials measuring CLD have been focused primarily on lens performance rather than specific characteristics or etiology of the discomfort experienced by the subject. Lessons learned from these published clinical trials nonetheless provide some guidance with respect to future clinical trial designs and performance to investigate CLD. Patient discomfort ranges from awareness of the lens, through sensation of dry eye, to actual pain. Impairment of visual function includes impairment of clarity, instability of vision, or fatigue in performing visual tasks.

Accurate assessment of the symptoms of CLD requires that clinical trial design include an appropriate and representative population of adequate size evaluated by questionnaires that specifically assess a particular clinical question symptom with well-controlled contact lens material, lens design, lens care products, and wearing schedule. Avoidance of bias is necessary in performance of the trial, including care in subject selection, implementation of random intervention group assignments, psychometric testing, and statistical analysis of the data.

At this time no specific clinical outcome instrument can be recommended on the basis of an evidence-based review of the

literature, but the CLDEQ-8 best approaches the most validated device.

Acknowledgments

Disclosure: Each workshop participant's disclosure data can be found in the Appendix of the Introduction.

References

- Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance. *Optom Vis Sci.* 2012; 89:1435-1442.
- Begley CG, Chalmers RL, Mitchell GL, et al. Characterization of ocular surface symptoms from optometric practices in North America. *Cornea.* 2001;20:610-618.
- Chalmers RL, Begley CG. Dryness symptoms among an unselected clinical population with and without contact lens wear. *Cont Lens Anterior Eye.* 2006;29:25-30.
- Donshik P. Giant papillary conjunctivitis. *Trans Am Ophthalmol Soc.* 1994;92:687-744.
- Donshik P, Ehlers W, Ballow M. Giant papillary conjunctivitis. *Immunol Allergy Clin North Am.* 2008;28:83-103.
- Ehlers W, Donshik P. Giant papillary conjunctivitis. *Curr Opin Allergy Clin Immunol.* 2008;8:445-449.
- Kalat JW. *Biological Psychology.* 9th ed. Stamford, CT: Cengage Learning; 2007.
- Lowery D, Fillingim R, Wright R. Sex differences and incentive effects on perceptual and cardiovascular responses to cold pressor pain. *Psychosom Med.* 2003;65:284-291.
- Chalmers R, Long B, Dillehay S, Begley C. Improving contact-lens related dryness symptoms with silicone hydrogel lenses. *Optom Vis Sci.* 2008;85:778-784.
- Versura P, Profazio V, Balducci N, Campos EC. Efficacy of two-month treatment with Xiloiol eyedrops for discomfort from disposable soft contact lenses. *Clin Ophthalmol.* 2010;4: 1035-1041.
- Yang SN, Tai YC, Sheedy JE, Kinoshita B, Lampa M, Kern JR. Comparative effect of lens care solutions on blink rate, ocular discomfort and visual performance. *Ophthalmic Physiol Opt.* 2012;32:412-420.
- Nichols JJ, Bickle KM, Zink RC, Schiewe MD, Haque RM, Nichols KK. Safety and efficacy of topical azithromycin ophthalmic solution 1.0% in the treatment of contact lens-related dry eye. *Eye Contact Lens.* 2012;38:73-79.
- Dumbleton KA, Chalmers RL, McNally J, Bayer S, Fonn D. Effect of lens base curve on subjective comfort and assessment of fit with silicone hydrogel continuous wear contact lenses. *Optom Vis Sci.* 2002;79:633-637.
- Fonn D, Dumbleton K. Dryness and discomfort with silicone hydrogel contact lenses. *Eye Contact Lens.* 2003;29:S101-S104; discussion S115-S118, S192-S194.
- Dumbleton K, Keir N, Moezzi A, Feng Y, Jones L, Fonn D. Objective and subjective responses in patients refitted to daily-wear silicone hydrogel contact lenses. *Optom Vis Sci.* 2006;83:758-768.
- Riley C, Chalmers RL, Pence N. The impact of lens choice in the relief of contact lens related symptoms and ocular surface findings. *Cont Lens Anterior Eye.* 2005;28:13-19.
- Riley C, Young G, Chalmers R. Prevalence of ocular surface symptoms, signs, and uncomfortable hours of wear in contact lens wearers: the effect of refitting with daily-wear silicone hydrogel lenses (senofilcon a). *Eye Contact Lens.* 2006;32:281-286.
- Barabino S, Rolando M, Camicione P, Chen W, Calabria G. Effects of a 0.9% sodium chloride ophthalmic solution on the ocular surface of symptomatic contact lens wearers. *Can J Ophthalmol.* 2005;40:45-50.
- Chen Q, Wang J, Shen M, et al. Tear menisci and ocular discomfort during daily contact lens wear in symptomatic wearers. *Invest Ophthalmol Vis Sci.* 2011;52:2175-2180.
- Lin P-Y, Tsai S-Y, Cheng C-Y, Liu J-H, Chou P, Hsu W-M. Prevalence of dry eye among an elderly Chinese population in Taiwan. *Ophthalmology.* 2003;110:1096-1101.
- Coles ML, Brennan NA, Shuley V, et al. The influence of lens conditioning on signs and symptoms with new hydrogel contact lenses. *Clin Exp Optom.* 2004;87:367-371.
- Epstein AB. Contact lens care products effect on corneal sensitivity and patient comfort. *Eye Contact Lens.* 2006;32: 128-132.
- Fahmy M, Long B, Giles T, Wang CH. Comfort-enhanced daily disposable contact lens reduces symptoms among weekly/monthly wear patients. *Eye Contact Lens.* 2010;36:215-219.
- Geldis JR, Nichols JJ. The impact of punctal occlusion on soft contact lens wearing comfort and the tear film. *Eye Contact Lens.* 2008;34:261-265.
- Nichols JJ, Mitchell GL, Nichols KK, Chalmers RL, Begley CG. The performance of the Contact Lens Dry Eye Questionnaire as a screening survey for contact lens-related dry eye. *Cornea.* 2002;21:469-475.
- Hom MM. Use of cyclosporine 0.05% ophthalmic emulsion for contact lens-intolerant patients. *Eye Contact Lens.* 2006; 32:109-111.
- Malet F, Karsenti D, Pouliquen P. Preservative-free ocular hydrating agents in symptomatic contact lens wearers: saline versus PVP solution. *Eye Contact Lens.* 2003;29:38-43.
- Ousler GW III, Anderson RT, Osborn KE. The effect of senofilcon A contact lenses compared to habitual contact lenses on ocular discomfort during exposure to a controlled adverse environment. *Curr Med Res Opin.* 2008;24:335-341.
- Ozkan J, Papas E. Lubricant effects on low Dk and silicone hydrogel lens comfort. *Optom Vis Sci.* 2008;85:773-777.
- Stahl U, Willcox M, Stapleton F. Role of hypo-osmotic saline drops in ocular comfort during contact lens wear. *Cont Lens Anterior Eye.* 2010;33:68-75.
- Stiegemeier MJ, Friederichs GJ, Hughes JL, Larsen S, Movic W, Potter WB. Clinical evaluation of a new multi-purpose disinfecting solution in symptomatic contact lens wearers. *Contact Lens Anterior Eye.* 2006;29:143-151.
- Lemp MA, Caffery B, Lebow K, et al. Omafilcon A (Proclear) soft contact lenses in a dry eye population. *CLAO J.* 1999;25: 40-47.
- Martin R, Sanchez I, de la Rosa C, et al. Differences in the daily symptoms associated with the silicone hydrogel contact lens wear. *Eye Contact Lens.* 2010;36:49-53.
- Dumbleton KA, Woods CA, Jones LW, Fonn D. Comfort and adaptation to silicone hydrogel lenses for daily wear. *Eye Contact Lens.* 2008;34:215-223.
- Fonn D, Situ P, Simpson T. Hydrogel lens dehydration and subjective comfort and dryness ratings in symptomatic and asymptomatic contact lens wearers. *Optom Vis Sci.* 1999;76: 700-704.
- Guillon M, Maissa C. Clinical acceptance of two multipurpose solutions: MPS containing HPMC versus citrate-based MPS without rubbing. *CLAO J.* 2002;28:186-191.
- Lazon de la Jara P, Papas E, Diec J, Naduvilath T, Willcox MD, Holden BA. Effect of lens care systems on the clinical performance of a contact lens. *Optom Vis Sci.* 2013;90:344-350.
- Lebow KA, Schachet JL. Evaluation of corneal staining and patient preference with use of three multi-purpose solutions and two brands of soft contact lenses. *Eye Contact Lens.* 2003;29:213-220.

39. Willen CM, McGwin G, Liu B, Owsley C, Rosenstiel C. Efficacy of cyclosporine 0.05% ophthalmic emulsion in contact lens wearers with dry eyes. *Eye Contact Lens*. 2008;34:43-45.
40. Belmonte C, Acosta MC, Gallar J. Neural basis of sensation in intact and injured corneas. *Exp Eye Res*. 2004;78:513-525.
41. Belmonte C, Aracil A, Acosta MC, Luna C, Gallar J. Nerves and sensations from the eye surface. *Ocul Surf*. 2004;2:248-253.
42. Fonn D. Targeting contact lens induced dryness and discomfort: what properties will make lenses more comfortable. *Optom Vis Sci*. 2007;84:279-285.
43. Finkelstein L. Widely-defined measurement—an analysis of challenges. *Measurement*. 2009;42:1270-1277.
44. Luce R. *Individual Choice Behavior: A Theoretical Analysis*. New York: Dover; 2005.
45. Engelhard G, Thorndike, Thurstone, and Rasch: a comparison of their methods of scaling psychological and educational tests. *Appl Psychol Meas*. 1984;8:21-38.
46. Borsboom D. *Measuring the Mind: Conceptual Issues in Contemporary Psychometrics*. Cambridge, UK: Cambridge University Press; 2005.
47. Swets J. Is there a threshold? *Science*. 1961;134:168-177.
48. Stevens S. Measurement and man. *Science*. 1958;127:383-389.
49. Frigerio A, Giordani A, Mari L. Outline of a general model of measurement. *Synthese*. 2009;175:123-149.
50. Pesudovs K, Garamendi E, Elliott D. The contact lens impact on quality of life (CLIQ) questionnaire: development and validation. *Invest Ophthalmol Vis Sci*. 2006;47:2789-2796.
51. Begley CG, Caffery B, Chalmers RL, Mitchell LG. Dry Eye Investigation (DREI) Study Group. Use of the dry eye questionnaire to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye. *Cornea*. 2002; 21:664-670.
52. Chalmers R, Begley C, Caffery B. Validation of the 5-item dry eye questionnaire (DEQ-5): discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Ant Eye*. 2010;33:55-60.
53. Baudouin C, Creuzot-Garcher C, Hoang-Xuan T, et al. Creating a specific diagnostic and quality-of-life questionnaire for patients with ocular surface disease. *J Fr Ophtalmol*. 2003;26:119-130.
54. Abetz L, Rajagopalan K, Mertzanis P, Begley C, Barnes R, Chalmers R. Development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients. *Health Qual Life Outcomes*. 2011;9:111.
55. McMonnies CW, Ho A. Responses to a dry eye questionnaire from a normal population. *J Am Optom Assoc*. 1987;58:588-591.
56. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol*. 2000;118:615-621.
57. Schaumberg DA, Gulati A, Mathers W, et al. Development and validation of a short global dry eye symptom index. *Ocul Surf*. 2007;5:50-57.
58. Simpson T, Situ P, Jones L, Fonn D. Dry eye symptoms assessed by four questionnaires. *Optom Vis Sci*. 2008;85:692-699.
59. Gulati A, Sullivan R, Buring JE, Sullivan DA, Dana R, Schaumberg DA. Validation and repeatability of a short questionnaire for dry eye syndrome. *Am J Ophthalmol*. 2006;142:125-131.
60. Donate J, Benitez Del Castillo JM, Fernandez C, Garcia Sanchez J. Validation of a questionnaire for the diagnosis of dry eye [in Spanish]. *Arch Soc Esp Ophthalmol*. 2002;77:493-500.
61. Blackie CA, Solomon J, Scaffidi RC, Greiner JV, Lemp MA, Korb DR. The relationship between dry eye symptoms and lipid layer thickness. *Cornea*. 2009;28:789-794.
62. Narayanan S, Miller W, Prager T, et al. The diagnosis and characteristics of moderate dry eye in non-contact lens wearers. *Eye Contact Lens*. 2005;31:96-104.
63. Sorbara L, Peterson R, Woods C, Fonn D. Multipurpose disinfecting solutions and their interactions with a silicone hydrogel lens. *Eye Contact Lens*. 2009;35:92-97.
64. Diec J, Evans VE, Tilia D, Naduvilath T, Holden BA, Lazon de la Jara P. Comparison of ocular comfort, vision, and SICS during silicone hydrogel contact lens daily wear. *Eye Contact Lens*. 2012;38:2-6.
65. Garofalo RJ, Dassanayake N, Carey C, Stein J, Stone R, David R. Corneal staining and subjective symptoms with multipurpose solutions as a function of time. *Eye Contact Lens*. 2005; 31:166-174.
66. Campbell R, Kame G, Leach N, Paul M, White E, Zigler L. Clinical benefits of a new multipurpose disinfecting solution in silicone hydrogel and soft contact lens users. *Eye Contact Lens*. 2012;38:93-101.
67. Diec J, Lazon de la Jara P, Willcox M, Holden BA. The clinical performance of lenses disposed of daily can vary considerably. *Eye Contact Lens*. 2012;38:313-318.
68. Peterson RC, Fonn D, Woods CA, Jones L. Impact of a rub and rinse on solution-induced corneal staining. *Optom Vis Sci*. 2010;87:1030-1036.
69. Jones L, MacDougall N, Sorbara LG. Asymptomatic corneal staining associated with the use of balafilcon silicone-hydrogel contact lenses disinfected with a polyaminopropyl biguanide-preserved care regimen. *Optom Vis Sci*. 2002;79: 753-761.
70. Walker J, Young G, Hunt C, Henderson T. Multi-centre evaluation of two daily disposable contact lenses. *Cont Lens Anterior Eye*. 2007;30:125-133.
71. Young G, Keir N, Hunt C, Woods CA. Clinical evaluation of long-term users of two contact lens care preservative systems. *Eye Contact Lens*. 2009;35:50-58.
72. Berry M, Pult H, Purslow C, Murphy PJ. Mucins and ocular signs in symptomatic and asymptomatic contact lens wear. *Optom Vis Sci*. 2008;85:930-938.
73. Peterson RC, Wolffsohn JS, Fowler CW. Optimization of anterior eye fluorescein viewing. *Am J Ophthalmol*. 2006; 142:572-575.
74. Morgan PB, Maldonado-Codina C. Corneal staining: do we really understand what we are seeing? *Cont Lens Anterior Eye*. 2009;32:48-54.
75. Nichols JJ, Sinnott LT. Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye. *Invest Ophthalmol Vis Sci*. 2006;47:1319-1328.
76. Efron N, Morgan PB, Katsara SS. Validation of grading scales for contact lens complications. *Ophthalmic Physiol Opt*. 2001;21:17-29.
77. Carnt NA, Evans VE, Naduvilath TJ, et al. Contact lens-related adverse events and the silicone hydrogel lenses and daily wear care system used. *Arch Ophthalmol*. 2009;127:1616-1623.
78. Bright FV, Merchea MM, Kraut ND, Maziarz EP, Liu XM, Awasthi AK. A preservative-and-fluorescein interaction model for benign multipurpose solution-associated transient corneal hyperfluorescence. *Cornea*. 2012;31:1480-1488.
79. Andrasko G, Ryen K. Corneal staining and comfort observed with traditional and silicone hydrogel lenses and multipurpose solution combinations. *Optometry*. 2008;79: 444-454.

80. Carnt N, Jalbert I, Stretton S, Naduvilath T, Papas E. Solution toxicity in soft contact lens daily wear is associated with corneal inflammation. *Optom Vis Sci.* 2007;84:309-315.
81. Lemp MA. Report of the National Eye Institute/industry workshop on clinical trials in dry eyes. *CLAO J.* 1995;21:221-232.
82. Maissa C, Guillon M, Garofalo RJ. Contact lens-induced circumlimbal staining in silicone hydrogel contact lenses worn on a daily wear basis. *Eye Contact Lens.* 2012;38:16-26.
83. Lakkis C, Brennan NA. Bulbar conjunctival fluorescein staining in hydrogel contact lens wearers. *CLAO J.* 1996;22:189-194.
84. Guillon M, Maissa C. Bulbar conjunctival staining in contact lens wearers and non lens wearers and its association with symptomatology. *Cont Lens Anterior Eye.* 2005;28:67-73.
85. Stahl U, Willcox MD, Naduvilath T, Stapleton F. Influence of tear film and contact lens osmolality on ocular comfort in contact lens wear. *Optom Vis Sci.* 2009;86:857-867.
86. Efron N. Grading scales for contact lens complications. In: Efron N, ed. *Contact Lens Practice.* Oxford: Butterworth-Heinemann; 2010.
87. CCLRU: CCLRU grading scales. In: Phillips A, Speedwell, L, eds. *Contact Lenses.* Oxford: Butterworth-Heinemann; 1997: 863-867.
88. Methodologies to diagnose and monitor dry eye disease. Report of the diagnostic methodology subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf.* 2007;5: 108-152.
89. Whitcher J, Shiboski C, Shiboski S, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol.* 2010;149:405-415.
90. Morgan PB, Chamberlain P, Moody K, Maldonado-Codina C. Ocular physiology and comfort in neophyte subjects fitted with daily disposable silicone hydrogel contact lenses. *Cont Lens Anterior Eye.* 2013;36:118-125.
91. Ozkan J, Ehrmann K, Meadows D, Lally J, Holden B, de la Jara PL. Lens parameter changes under in vitro and ex vivo conditions and their effect on the conjunctiva. *Cont Lens Anterior Eye.* 2013;36:171-175.
92. Korb DR, Greiner JV, Herman JP, et al. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. *CLAO J.* 2002;28:211-216.
93. Knop E, Knop N, Zhivov A, et al. The lid wiper and mucocutaneous junction anatomy of the human eyelid margins: an in vivo confocal and histological study. *J Anat.* 2011;218:449-461.
94. Korb DR, Herman JP, Greiner JV, et al. Lid wiper epitheliopathy and dry eye symptoms. *Eye Contact Lens.* 2005;31:2-8.
95. Sweeney D, du Toit RK, L, Jalbert I, et al. Clinical performance of silicone hydrogel lenses. In: Sweeney D, ed. *Silicone Hydrogels: Continuous Wear Contact Lenses.* Oxford: Butterworth-Heinemann; 2004:164-216.
96. Hoh H, Schirra F, Kienecker C, Ruprecht KW. Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye [in German]. *Ophthalmologie.* 1995;92:802-808.
97. Pult H, Purslow C, Berry M, Murphy P. Clinical tests for successful contact lens wear. *Optom Vis Sci.* 2008;85:924-929.
98. Pult H, Murphy PJ, Purslow C. A novel method to predict the dry eye symptoms in new contact lens wearers. *Optom Vis Sci.* 2009;86:E1042-E1050.
99. Maldonado-Codina C, Morgan PB, Schnider CM, Efron N. Short-term physiologic response in neophyte subjects fitted with hydrogel and silicone hydrogel contact lenses. *Optom Vis Sci.* 2004;81:911-921.
100. Santodomingo-Rubido J, Wolffsohn JS, Gilmartin B. Changes in ocular physiology, tear film characteristics, and symptomatology with 18 months silicone hydrogel contact lens wear. *Optom Vis Sci.* 2006;83:73-81.
101. Papas E. On the relationship between soft contact lens oxygen transmissibility and induced limbal hyperaemia. *Exp Eye Res.* 1998;67:125-131.
102. Michaud L, Giasson CJ. Overwear of contact lenses: increased severity of clinical signs as a function of protein adsorption. *Optom Vis Sci.* 2002;79:184-192.
103. Young G, Coleman S. Poorly fitting soft lenses affect ocular integrity. *CLAO J.* 2001;27:68-74.
104. Glasson M, Stapleton F, Willcox MDP. The effect of contact lens wear on the tear film and ocular surface characteristics of tolerant and intolerant wearers. *Contact Lens Anterior Eye.* 2006;29:41-47.
105. Guillon M, Maissa C. Use of silicone hydrogel material for daily wear. *Cont Lens Anterior Eye.* 2007;30:5-10, quiz 71.
106. Subbaraman LN, Glasier MA, Varikooty J, Srinivasan S, Jones L. Protein deposition and clinical symptoms in daily wear of etafilcon lenses. *Optom Vis Sci.* 2012;89:1450-1459.
107. Glasson MJ, Stapleton F, Keay L, Sweeney D, Willcox MD. Differences in clinical parameters and tear film of tolerant and intolerant contact lens wearers. *Invest Ophthalmol Vis Sci.* 2003;44:5116-5124.
108. Guillon M, Styles E, Guillon J, Maissa C. Preocular tear film characteristics of nonwearers and soft contact lens wearers. *Optom Vis Sci.* 1997;74:273-279.
109. Keir N, Jones L. Wettability and silicone hydrogel lenses: a review. *Eye Contact Lens.* 2013;39:100-108.
110. Cho P, Ho KY, Huang YC, Chui HY, Kwan MC. Comparison of noninvasive tear break-up time measurements from black and white background instruments. *Optom Vis Sci.* 2004;81: 436-441.
111. Yokoi N, Takehisa Y, Kinoshita S. Correlation of tear lipid layer interference patterns with the diagnosis and severity of dry eye. *Am J Ophthalmol.* 1996;122:818-824.
112. Craig JP, Tomlinson A. Importance of the lipid layer in human tear film stability and evaporation. *Optom Vis Sci.* 1997;74:8-13.
113. Guillon M, Maissa C. Contact lens wear affects tear film evaporation. *Eye Contact Lens.* 2008;34:326-330.
114. Sarac O, Gurdal C, Bostanci-Ceran B, Can I. Comparison of tear osmolarity and ocular comfort between daily disposable contact lenses: hilafilcon B hydrogel versus narafilcon A silicone hydrogel. *Int Ophthalmol.* 2012;32:229-233.
115. Kojima T, Matsumoto Y, Ibrahim OM, et al. Effect of controlled adverse chamber environment exposure on tear functions in silicon hydrogel and hydrogel soft contact lens wearers. *Invest Ophthalmol Vis Sci.* 2011;52:8811-8817.
116. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol.* 2011;151:792-798, e791.
117. Shen J, Thibos LN. Peripheral aberrations and image quality for contact lens correction. *Optom Vis Sci.* 2011;88:1196-1205.
118. Jiang H, Wang D, Yang L, Xie P, He JC. A comparison of wavefront aberrations in eyes wearing different types of soft contact lenses. *Optom Vis Sci.* 2006;83:769-774.
119. Tutt R, Bradley A, Begley C, Thibos LN. Optical and visual impact of tear break-up in human eyes. *Invest Ophthalmol Vis Sci.* 2000;41:4117-4123.
120. Thai LC, Tomlinson A, Ridder WH. Contact lens drying and visual performance: the vision cycle with contact lenses. *Optom Vis Sci.* 2002;79:381-388.
121. Chen J, Simpson TL. A role of corneal mechanical adaptation

- in contact lens-related dry eye symptoms. *Invest Ophthalmol Vis Sci.* 2011;52:1200-1205.
122. Liu Q, McDermott AM, Miller WL. Elevated nerve growth factor in dry eye associated with established contact lens wear. *Eye Contact Lens.* 2009;35:232-237.
 123. Situ P, Simpson TL, Jones LW, Fonn D. Conjunctival and corneal hyperesthesia in subjects with dryness symptoms. *Optom Vis Sci.* 2008;85:867-872.
 124. Hatfield RO, Jordan DR, Bennett ES, Henry VA, Marohn JW, Morgan BW. Initial comfort and surface wettability: a comparison between different contact lens materials. *J Am Optom Assoc.* 1993;64:271-273.
 125. Tonge S, Jones L, Goodall S, Tighe B. The ex vivo wettability of soft contact lenses. *Curr Eye Res.* 2001;23:51-59.
 126. Zhao Z, Naduvilath T, Flanagan JL, et al. Contact lens deposits, adverse responses, and clinical ocular surface parameters. *Optom Vis Sci.* 2010;87:669-674.
 127. Lipener C. A randomized clinical comparison of OPTI-FREE EXPRESS and ReNu MultiPLUS multipurpose lens care solutions. *Adv Ther.* 2009;26:435-446.
 128. Dillehay SM, Miller MB. Performance of Lotrafilcon B silicone hydrogel contact lenses in experienced low-Dk/t daily lens wearers. *Eye Contact Lens.* 2007;33:272-277.
 129. Brennan NA, Coles ML, Connor HR, McIlroy RGA. 12-month prospective clinical trial of comfilcon A silicone-hydrogel contact lenses worn on a 30-day continuous wear basis. *Cont Lens Anterior Eye.* 2007;30:108-118.
 130. Brennan NA, Coles ML, Ang JH. An evaluation of silicone-hydrogel lenses worn on a daily wear basis. *Clin Exp Optom.* 2006;89:18-25.
 131. Brennan NA, Coles ML, Comstock TL, Levy BA. 1-year prospective clinical trial of balafilcon a (PureVision) silicone-hydrogel contact lenses used on a 30-day continuous wear schedule. *Ophthalmology.* 2002;109:1172-1177.
 132. Wolffsohn JS, Hunt OA, Chowdhury A. Objective clinical performance of "comfort-enhanced" daily disposable soft contact lenses. *Cont Lens Anterior Eye.* 2010;33:88-92.
 133. Peterson RC, Wolffsohn JS, Nick J, Winterton L, Lally J. Clinical performance of daily disposable soft contact lenses using sustained release technology. *Cont Lens Anterior Eye.* 2006;29:127-134.
 134. Michel M, Sickenberger W, Pult H. The effectiveness of questionnaires in the determination of contact lens induced dry eye. *Ophthalmic Physiol Opt.* 2009;29:479-486.
 135. Young G, Chalmers R, Napier L, Kern J, Hunt C, Dumbleton K. Soft contact lens-related dryness with and without clinical signs. *Optom Vis Sci.* 2012;89:1125-1132.
 136. Design and conduct of clinical trials. Report of the Clinical Trials Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf.* 2007;5:153-162.
 137. Schulz K, Altman D, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med.* 2010;152:726-732.
 138. Keir N, Woods CA, Dumbleton K, Jones L. Clinical performance of different care systems with silicone hydrogel contact lenses. *Cont Lens Anterior Eye.* 2010;33:189-195.
 139. Tilia D, de la Jara PL, Peng N, Papas E, Holden B. Effect of lens and solution choice on the comfort of contact lens wearers. *Optom Vis Sci.* 2013;90:411-418.
 140. Naglie G, Tomlinson G, Tansey C, et al. Utility-based quality of life measures in Alzheimer's disease. *Qual Life Res.* 2006;15:631-643.
 141. Rothwell P. External validity of randomised controlled trials: to whom do the results of this trial apply? *Lancet.* 2005;365:82-89.
 142. Stone A, Shiffman S, Schwartz J, Broderick J, Hufford M. Patient compliance with paper and electronic diaries. *Control Clin Trials.* 2003;24:182-199.
 143. Stratton R, Stubbs R, Hughes D, King N, Blundell J, Elia M. Comparison of the traditional paper visual analogue scale questionnaire with an Apple Newton electronic appetite rating system (EARS) in free living subjects feeding ad libitum. *Eur J Clin Nutr.* 1998;52:737-741.
 144. Stubbs R, Hughes D, Johnstone A, et al. The use of visual analogue scales to assess motivation to eat in human subjects: a review of their reliability and validity with an evaluation of new hand-held computerized systems for temporal tracking of appetite ratings. *Br J Nutr.* 2000;84:405-415.
 145. Morgan P, Maldonado-Codina C, Chatterjee N, Moody K. Elicitation of subjective responses via sms (text) messaging in contact lens clinical trials (E-Abstract 075143). *Optom Vis Sci.* 2007;84.
 146. Plowright A, Morgan P, Maldonado-Codina C, Moody K. An investigation of ocular comfort in contact lens wearers, spectacle wearers and non-wearers (E-abstract 85050). *Optom Vis Sci.* 2008;85.
 147. Woods C, Dumbleton K, Jones L, Fonn D. Patient use of smartphones to communicate subjective data in clinical trials. *Optom Vis Sci.* 2011;88:290-294.
 148. Axen I, Bodin L, Bergstrom G, et al. The use of weekly text messaging over 6 months was a feasible method for monitoring the clinical course of low back pain in patients seeking chiropractic care. *J Clin Epidemiol.* 2012;65:454-461.
 149. Keir N, Richter D, Luensmann D, et al. The effect of masking on subjective results with daily disposable contact lenses (E-abstract 110290). *Optom Vis Sci.* 2011;88.
 150. Juni P, Altman D, Egger M. Assessing the quality of controlled clinical trials. *Br Med J.* 2001;323:42-46.
 151. Moerman D, Jonas W. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med.* 2002;136:471-476.
 152. Kennedy W. The nocebo reaction. *Medical World.* 1961;95:203-205.
 153. Dumbleton KA, Woods M, Woods CA, Jones LW, Fonn D. Ability of patients to recall habitual contact lens products and enhancement of recall using photographic aids. *Cont Lens Anterior Eye.* 2011;34:236-240.
 154. Moore DS, McCabe DGP. *Introduction to the Practice of Statistics.* 5th ed. New York: W.H. Freeman & Company; 2005.
 155. Good J, Mittal Y. The amalgamation and geometry of two-by-two contingency tables. *Ann Stat.* 1987;15:694-711.
 156. Pearl J. *Causality: Models, Reasoning, and Inference.* 2nd ed. Cambridge: Cambridge University Press; 2009.
 157. Bickel P, Hammel E, O'Connell J. Sex bias in graduate admissions: data from Berkeley. *Science.* 1975;187:398-404.
 158. Barnett A, van der Pols J, Dobson A. Regression to the mean: what it is and how to deal with it. *Int J Epidemiol.* 2005;34:215-220.
 159. Stahl U, Willcox MDP, Naduvilath T, Stapleton F. The influence of tear film and contact lens osmolality on ocular comfort during short-term contact lens wear. *Optom Vis Sci.* 2009;86:857-867.