Appendix 2. Functional groupings of tests used in the assessment of dry eye

- **1. Symptoms tests**
  - *Questionnaires*
    - NEI-VFQ25
    - McMonnies
    - Schein
    - McCarty
    - OSDI
    - DEQ
    - IDEEL
  - ***Visual function***
    - LogMar acuity
    - Contrast sensitivity
    - Functional visual acuity
- **2. Aqueous tears**
  - ***Tear volume***
    - Fluorimetry
    - Hamano thread
    - Periotron test—"basal tear volume"
  - ***Tear meniscus***
    - Radius of curvature
    - Height
    - Area of cross-section
  - ***Tear film thickness***
  - ***Tear flow***
    - Fluoroimetry
    - Schirmer test
      - Schirmer I
      - Dynamic Schirmer
      - Schirmer II
      - Reflex Schirmer
      - Electronic
  - ***Tear turnover***
    - Dye dilution
    - Tear clearance
    - Fluorimetry
  - ***Tear evaporation***
    - Evaporimetry
- **3. Tear stability and visual function**
  - ***Visual acuity***
    - ETDRS
    - Functional visual acuity
  - ***Tear stability***
    - Breakup time (BUT)
    - SBUT: Symptomatic BUT
    - Tear film BUT fluorescein
    - Noninvasive BUT (NIBUT)
    - Tear thinning time
    - Topographic analysis
    - Tear stability analysis system
    - Wavefront analysis
- **4. Tear composition**
  - ***Biological fluids***
    - Aqueous tears
      - Lactoferrin
      - Lysozyme
      - Peroxidase
      - Immunoglobulin A
        - Ceruloplasmin
        - Inflammatory mediators
        - Matrix metalloproteinases
        - Other proteins
        - Mucins
        - Lipids
  - ***Cells in biofluids***
    - Inflammatory cells
      - Epithelial cells
      - Tear debris
  - ***Surface cells***
    - Impression cytology
    - Flow cytometry
    - Brush cytology
    - Confocal microscopy
  - ***Meibomian lipids***
    - Evaporimetry
    - Interferometry
    - Thickness
    - Grading
    - Meibometry (casual delivery)
    - Meibography
    - Morphology in MGD
    - Expressed oil quality
    - Lipid chemistry
  - ***Tears: physical***
    - Osmolarity
      - Depression of freeze point
      - Vapor pressure osmometry
      - Conductivity OcuSense
      - Electrolyte composition
    - Tear ferning
  - ***Surface damage***
    - Grading staining
    - Fluorescein stain
    - Rose Bengal stain
    - Lissamine green
    - Double staining
- **5. Other criteria**
  - Tear function index (TFI)
  - Ocular protection index (OPI)
  - Conjunctivochalasis score
  - Blink characteristics
  - Distinction from allergy
  - Lid margin disease criteria
  - Microbiology and lid disease
- **6. Sjogren syndrome**
  - Serological tests
    - Anti-Ro
    - Anti-La
    - Anti-M3 receptor
    - Anti-fodrin
    - Minor salivary gland biopsy
    - Lacrimal gland biopsy
    - Systemic endocrine findings
  - Tests of salivary function
    - Biscuit test
    - Sialography
- **7. Tests for assorted disorders**
  - Wegener's: Positive ANCA
  - Rheumatoid arthritis: Positive Rh-F
  - Systemic lupus erythmatosus: ????
  - LASIK dry eye neuro-epitheliopathy: Composite clinical findings

Appendix 3. A proforma diagnostic template

DEW	Dry Eye: Diagnostic Test Template	
Rapporteur	Please insert your name	Date: DD/MM/YY
Reviewers	Names of additional reviewers added here	
Name of test	eg, Schirmer I	
To diagnose	*Test used to diagnose—eg, aqueous tear deficiency (ATD)*	REFERENCES
Version of test	[V] *Please call your preferred version, version 1. Other versions should be submitted on separate templates and numbered, not necessarily in priority order.*	*Please reference the source of this version*
Description	*This should be a one or two line statement saying what the test is for*	
Nature of study	*If you wish to refer to a specific study in detail, enter the details here*	
Conduct of test	*Please describe all steps of the test in sufficient detail to provide a template for a trainer*	
Results of study	*If you have described a specific study in detail, place the results here*	
Web video	Available [ ] *If instruction would be aided by a video of the technique, please tick this video box.*	
Materials	Please list the nature and sources of materials used for the test as described.	
Variations of technique		
Standardization	Time of day [ ] Temperature [ ] Humidity [ ] Air speed [ ] Illumination [ ] Other: [ ] *Tick the boxes if you think that such standardization would improve the repeatability of the test.*	
Diagnostic value	This version: [ ] Other version: [ ] *Please state if these stats relate to this version or another cited version. Please cite statistics indicating the diagnostic value of the test in a referenced study.*	*Please cite reference to stats used*
Repeatability	Intra-observer agreement. [ ] Inter-observer agreement. [ ]	
Sensitivity	**(true positives)** [ ]	
Specificity	**(100 – false positives)** [ ]	
Other stats	*If you have other stats for this or related versions of the test, add as many rows as necessary and cite the reference.*	
Level of evidence		
Test problems	*Is there a problem with this test?*	
Test solutions	*Can you suggest an improvement?*	
Forward look	*What future developments do you foresee?*	
Glossary	*Please explain abbreviations.*	

References: [To be inserted]

Appendix 4. A note on the Japanese criteria for dry eye diagnosis

The previous Japanese dry eye diagnostic criteria were revised by the Japanese Dry Eye Research Society after the 1994-95 NEI/Industry workshop. (AU: INSERT JAPANESE REFERENCE.) The criteria, unpublished in the English literature, omitted symptoms from the diagnostic criteria at that time, because objective and subjective findings did not appear to correlate. Following the DEWS meeting of 2004, the importance of symptoms was accepted in Japan and the criteria have been modified.

The Japanese criteria prior to the 2004 DEWS meeting were:

1) Qualitative or quantitative disturbance of the tear film (quantity: Schirmer test less than 5 mm or phenol red thread test less than 10 mm; quality: BUT less than 5 sec)
2) Conjunctivocorneal epithelial damage (excluding all other etiologies other than that listed under number 1)
   Fluorescein staining greater than 1 point
   RB staining greater than 3 points
   (The presence of either fluorescein or RB staining is finding sufficient to satisfy criterion number 2)

The presence of both 1 and 2 = Definite dry eye. Presence of 1 or 2 = Probable dry eye

The Japanese diagnostic criteria have been revised by the Japan Dry Eye Research Society in August 2005, to include symptoms, as follows.

New Diagnostic Criteria of the Japan Dry Eye Research Society: Revised in August 2005			
	Definite DE	Probable DE	Possible DE
Symptoms	Yes	Yes	Yes
Tear film quality/quantity—disturbed	Yes	No	Yes
Epithelial damage	Yes	Yes	No

The phenol red thread test has been removed from the diagnostic criteria.
A fluorescein staining score of above 3 points is now required as positive staining (instead of 1 point).

Design and Conduct of Clinical Trials:
Report of the Clinical Trials Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **This report summarizes some universal concepts with regard to clinical trials in general and other issues pertaining to clinical trials specifically tailored to the study of therapeutic intervention in dry eye disease. The report also makes recommendations for logistical design and implementation of such trials. It identifies peculiarities of dry eye disease that complicate clinical trial design, such as the lack of correlation of signs and symptoms, as well as the likelihood of control interventions having a lubricant (placebo) effect. Strategies for environmental trials and controlled adverse environment trials are reviewed.**

KEY WORDS **clinical trials, DEWS, dry eye, Dry Eye WorkShop**

I. INTRODUCTION

Clinical trials in dry eye disease represent a challenge to clinicians, epidemiologists, and biostatisticians, as well as to those seeking regulatory approval for medications or other therapies.[1] This report summarizes some universal concepts with regard to clinical trials in general and addresses other issues pertaining to clinical trials specifically tailored to the study of therapeutic intervention in dry eye disease. The level of evidence for supporting data from clinical trials is identified in the bibliography, according to the modified American Academy of Ophthalmology Preferred Practices guidelines. The report also makes recommendations for logistical design and implementation of such trials.

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Proprietary interests of Subcommittee members are disclosed on pages (EDITOR; INSERT PAGE NUMBERS)

Reprints are not available. Articles can be accessed at: (EDITOR: INSERT TFOS WEB SITE INFO)

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II. GOALS OF THE CLINICAL TRIALS SUBCOMMITTEE

The goals of the Clinical Trials Subcommittee were to systematically review literature, procedures, and concepts related to clinical trials in general, to consider special issues related to clinical trials involving therapeutic interventions in dry eye disease, and to present guidelines for successful conduct of clinical trials.

III. GUIDELINES FOR CLINICAL TRIALS IN GENERAL

Before a clinical trial is initiated, a state of equipoise must exist. In other words, there must be sufficient doubt about the effectiveness of the particular intervention under consideration to justify withholding it from a portion of the study subjects, and, at the same time, there must be sufficient belief in the therapeutic potential of the intervention to justify its exposure to the remaining portion of willing and eligible study participants. If these conditions are met, then a number of additional issues need to be considered in the design and conduct of the clinical trial so that valid results can be obtained (Table 1). Important processes include formulation of a concise and specific study question, specification of the primary outcome measure, statistical estimation of the necessary sample-size, specification of the length of follow-up and specific schedule for baseline and follow-up evaluations, selection of the study population, definition of the primary outcome measure, random allocation of the intervention(s)/treatment(s), establishment of strategies for maintenance of compliance with the allocated intervention(s)/treatment(s) and for achievement of high and balanced rates of follow-up. In addition, it is important to establish an organizational and decision-making structure and specific procedures for intake of data, and for patient safety monitoring.

A. Design

The most desirable design of a clinical trial is a prospective, randomized, double-masked, placebo- or vehicle- con-

OUTLINE

I. Introduction
II. Goals of the Clinical Trials Subcommittee
III. Guidelines for clinical trials in general
  A. Design
  B. Inclusion and exclusion criteria
  C. Outcome measures
  D. Sample size, randomization and data analysis
  E. Administration of a clinical trial
IV. Guidelines for clinical trials in dry eye
V. Observations from previous clinical trials in dry eye
  A. Peculiarities of clinical trials in dry eye
  B. Evaluation and outcome parameters
  C. Suggested attributes of clinical trials in dry eye
VI. Features to facilitate multicenter and international collaborative clinical trials

trolled parallel group or crossover study. Other acceptable designs include equivalence or superiority trials to compare a new therapy to one that is already approved or in common use. Such trials must also be constructed as prospective, randomized, masked trials.[2-5] Parallel group studies should ideally provide for demographic and environmental climate or activity comparability. With large enough sample size, randomization will tend to ensure equal distribution of demographic characteristics across treatment groups. If there is a particular concern with regard to one or more demographic factors (eg, sex, age), then equal distribution of these factors across treatment groups can be achieved by randomizing in small blocks. Unfortunately, this technique generally is impractical to implement and adds considerably to the number of patients that must be screened to find suitable matches.

In general, crossover design trials have the benefit of using the patient as their own control but are fraught with confounding problems when, as with dry eye, the potential exists for the persistent effects of one treatment to outlast that of another. Also, if one treatment interferes with another, the sequential effects of the test medications or treatments could be confounding. Three assumptions are inherent in a crossover study:

1) The treatment does not cure the disease.
2) There is no carryover between periods.
3) In order to contribute to the analysis, all patients must complete all periods.

The perceived benefit of a crossover study over a parallel study is based upon an assumption that *intra*-patient variability is less than *inter*-patient variability. This is not always true. Washout periods with placebo treatment can be used to abrogate the lingering effects of prior therapy, but the duration of the washout period must be sufficient for effective washout, and the sufficient duration may be unknown or vary, depending upon the specific agents tested. Given these concerns, an important compensatory design strategy in crossover trials is to randomize the sequence of administration of the test agent and control agent, so that some individuals will receive the active therapy first, whereas others will receive the control therapy first.

Table 1. Attributes of well-designed clinical trial

1. Formulation of a concise and specific study question
2. Specification of a primary outcome measure
3. Statistical estimation of the necessary sample-size
4. Specification of the length of follow-up and specific schedule for baseline and follow-up evaluations
5. Selection of the study population
6. Definition of the primary outcome measure
7. Random allocation of the intervention(s)/treatment(s)
8. Strategies for maintenance of compliance with the allocated intervention(s)/treatment(s), and for the achievement of high and balanced rates of follow-up
9. Establishment of an organizational and decision-making structure
10. Specification of procedures for intake of data and for patient safety monitoring

B. Inclusion and Exclusion Criteria

Appropriate inclusion and exclusion criteria are essential to assure the integrity of the trial. Inclusion criteria should identify a number of appropriate variables specifically to define the population that will be studied (Table 2). Such criteria generally include 1) the ability of subjects to provide informed consent, 2) the ability to comply with the protocol, and 3) the existence of disease severity sufficient to demonstrate a statistically significant and clinically meaningful effect of therapy. Specific diagnostic criteria are usually defined to ensure homogeneity of disease status, which can lead to a more precise study.

Exclusion criteria may be used to exclude, for example, 1) subjects with concurrent disease that could confound the response to therapy, 2) subjects unlikely to comply with the protocol or likely to be lost to follow-up, and 3) subjects with known hypersensitivity or intolerance to the proposed therapy (Table 3).

When selecting inclusion and exclusion criteria, the

Table 2. Inclusion criteria for clinical trial

1. Subjects must be capable of providing informed consent.
2. Subjects must be able to comply with the protocol.
3. Disease severity must be sufficient to demonstrate a statistically significant and clinically meaningful effect of therapy.
4. Specific diagnostic criteria must be defined to ensure homogeneity of disease status, which can lead to a more precise study.
5. Subjects must be capable of responding to the proposed mechanism of action of the intervention to be studied

Table 3. Exclusion criteria for clinical trial

1. Subjects have concurrent disease that could confound the response to therapy.
2. Subjects are unlikely to comply with the protocol or likely to be lost to follow-up.
3. Subjects have known hypersensitivity or intolerance to the proposed therapy.
4. Subjects use concomitant therapy that affects either tear function or ocular surface integrity.
5. Subjects have had surgical or other manipulation of the eye that could confound the outcome parameters or interfere with the mechanism of action of the proposed intervention to be studied.

investigator should be aware of the inherent trade-offs between the internal validity of the trial and its generalizability to the larger population of people with the disease of interest. Minimally restrictive inclusion and exclusion criteria make recruitment easier and provide a wider basis for generalization of the study findings, but treatment effects may be obscured by heterogeneity of disease status.

C. Outcome Measures

The outcome measure used to compare treatments may be either a clinical event or a surrogate outcome measure. The primary outcome measure should be selected prior to the start of data collection, as its rate of occurrence will affect various aspects of the study design, including the length of the study and the sample size. Although some clinical trials have employed post-hoc analysis of outcome variables, regulatory agencies are often reluctant to accept such analyses in pivotal trials. However, it is appropriate for most trials additionally to collect and analyze information on a number of secondary outcome measures. These can provide further information that may contribute to the overall evaluation of the study treatments.

Surrogate outcome measures are measurable features of the disease that reliably reflect an outcome parameter that is clinically relevant but difficult to precisely determine. For example, measurement of frequency of required instillation of comfort drops can be a quantifiable surrogate subjective measure of frequency/duration of discomfort occurring during the day. Similarly, an objective surrogate measure of tear film osmolarity could be the electrical conductivity of a tear sample. The surrogate outcome measure must be validated as a reliable and relevant monitor of outcome, but it may be of special value in a condition such as dry eye, where the correlation of signs and symptoms is weak, and objective evidence of change in disease is needed.

D. Sample Size, Randomization and Data Analysis

The sample size of a clinical trial should be sufficient to allow for a statistically powerful analysis of the primary study hypothesis. It may also provide for statistical comparisons within subgroups, if this is considered desirable or necessary to clarify the therapeutic response. It is essential that the trial be of sufficient size to provide power to detect a clinically meaningful treatment effect, as well as a statistically significant effect. Statistical analysis must be appropriate for the size, design, outcome measure(s), and duration of the study. The power to detect a given difference between treatments is directly proportional to the sample size and treatment difference, and indirectly proportional to the alpha level and variability. A key factor is the study planners' selection of a clinically significant difference. Then, they can determine the required number of patients to detect a difference that is at least that large, given that it exists.

Randomization to test or control treatment is generally the best strategy available in clinical trials to guard against treatment selection bias. There are numerous methods for establishing randomization. Today, most researchers use computer-generated randomization lists, which may be further stratified by study site and a pre-study characteristic (eg, disease severity). A written description of the randomization scheme used to generate treatment allocations should be recorded. This description should include sufficient detail to allow a person to reproduce the allocation schedule, and the assignment process should establish a clear audit trail.

Treatment assignments should be masked to the patient, physician, and the person issuing the assignment, until the patient has been officially enrolled and randomized into the study. Preferably, the study should be masked for patients and physicians until it is completed. This may be easiest to implement if assignments are issued by a person or group located outside of the clinic. Investigators should also be aware, particularly in small studies, that a randomization bias could occur that must be controlled or evaluated. The baseline characteristics of the study groups may also vary by chance, and if large enough, such differences can impact treatment comparisons. The strategy for the analysis of clinical trial data must be outlined in advance and must accommodate the form of the specified outcome variable(s) with appropriate methods of analysis.

The key feature in the analysis of clinical trials is adherence to the principle of "intention-to-treat." That is, the primary analysis of data in a trial must be conducted by classifying study subjects based on the original treatment to which they were assigned, regardless of the treatment they actually received or their adherence to the study protocol (Table 4). Good clinical practice dictates that assessment of qualifying patients and visits be made by the clinical management (ie, organization team) prior to unmasking of the treatment assignment. Furthermore, it should be stated a priori in the protocol and statistical analysis plan which

Table 4. Data analysis: populations to analyze

1. Intent to Treat (ITT): All subjects randomized.
2. Modified Intent to Treat (Mod ITT): All subjects randomized who received at least one dose of medication
3. Per Protocol (PP): All subjects randomized who completed the treatment according to protocol

population is primary.

Statistical methods can be used to address missing data, eg, *last observation carried forward* (**LOCF**) or end-point substitution. Ideally, the efficacy and safety results from all populations will be in general agreement. However, differences may occur, for example, when subjects drop out due to efficacy failure or safety issues. Treatment cross-over, poor compliance, and loss to follow-up are key threats to the validity of a clinical trial, and every effort should be made to ensure adherence to the study protocol and follow-up that is as complete as possible. In the presence of losses to follow-up, a series of analyses are usually conducted under various assumptions regarding the rate of events among patients lost to follow-up. Similarly, secondary analyses can account for treatment received, as well as for differences in compliance, but these are not a substitute for the primary "intention-to-treat" analysis.

Basic analytic methods for clinical trials can be found in any number of biostatistical textbooks and other resources. Outcome analyses based on comparisons of the proportion of patients who have experienced the outcome of interest are a common method for analyzing trial data. They are generally valid as long as the intensity of follow-up is comparable in the two treatment groups, losses to follow-up are low, and the treatment groups have comparable baseline characteristics.

Statistical evaluation of the difference in proportions can be carried out using Fisher's exact test, or a chi-square test, if appropriate. However, simple analysis of the proportion of patients who experience the outcome fails to take into account the length of follow-up. This may become important in the setting of many clinical trials in which patients are recruited over an extended period of time and then followed through a specific calendar time point, resulting in varying lengths of patient follow-up. Analysis of data from such studies is usually approached using lifetable analyses methods, which provide a statistical means of dealing with the variable lengths of follow-up. Adjustment for differences in baseline characteristics can be approached by either stratification or multivariable analysis. Investigators should be aware that the issue of what constitutes statistical significance is complex, and they should interpret *P*-values with caution, particularly as most trials will provide data on a number of outcome measures. These statistical comparisons cannot be considered to be mutually independent. Consideration of appropriate adjustment for multiple comparisons is imperative.

E. Administration of a Clinical Trial

Organization and administration of a clinical trial is critical to success. An organizational structure is desirable for large, multi-center clinical trials. An exemplary organizational chart is shown in Figure 1.

Advance preparation and written standardized procedures are needed for each step in the conduct of a clinical trial in order to avoid the high risk of error or missing data. Appendices cited at the end of this chapter can be accessed at: www (**EDITOR: INSERT TFOS SITE ACCESS INFO**). A Manual of Procedures should be prepared. Elements of an adequate manual are listed in Appendix 1.[6-11]

Standards of Good Clinical Practice should be exercised for quality assurance. Guidelines for sponsors and investigators are detailed in Appendix 2 and include observation of regulatory requirements, including 1) sponsor's role, 2) investigator's role, 3) clinical and functional investigation laboratory's role, 4) ethics committee or committee for the protection of persons, 5) International Conference on Harmonization, and 6) regulatory guidelines.[12-30] It is appropriate to prepare an Investigator's Brochure for the tested drug (Appendix 3).[31] Use of the investigational medical product should be outlined (Appendix 4).[32-36] Adverse events and their management should be identified (Appendix 5).[37-43] The ethics approval process should be conducted through institutional or designated Institutional Review Boards appropriate to the investigator. Data from clinical trials should be made available after completion of the study and data analysis.[43]

IV. GUIDELINES FOR CLINICAL TRIALS IN DRY EYE DISEASE

General considerations for clinical trials in dry eye incorporate the key concepts delineated for clinical trials in general. Clinical trials in dry eye disease can include prospective environmental and prospective challenge designs. A protocol customized to the hypothesized mechanism of action of the drug or intervention to be tested is desirable.

An environmental trial should embrace the general design guidelines listed above with prospective, randomized, double-masked, placebo/vehicle controlled features. There should be adequate duration of study to demonstrate efficacy and safety.

Inclusion and exclusion criteria should identify a potentially responsive population and be selected to avoid or minimize regression to the mean or observation bias. This approach should exclude: 1) the presence or absence of any ocular surface disease that would cause dry eyes other than the condition for which the drug or device is being tested; 2) the presence or absence of a dry eye-associated systemic disease other than the primary condition causing dry eyes; 3) use of systemic medications with possible influence on the tear film, tear secretion, or ocular surface; 4) use of concomitant or previous topical eye medications that would alter the effect of the drug or device being evaluated; 5) history of previous ocular surgery, including refractive surgery, eyelid tattooing, eyelid surgery, or corneal surgery; 6) the presence or absence of associated meibomian gland disease appropriate to study parameters; and 7) the presence or absence of contact lens wear. When patients are on a stable regimen of lubricant therapy that does not specifically interfere with the mechanism of action of the formulation of drug or intervention to be tested, it may be acceptable to enroll such patients while they continue

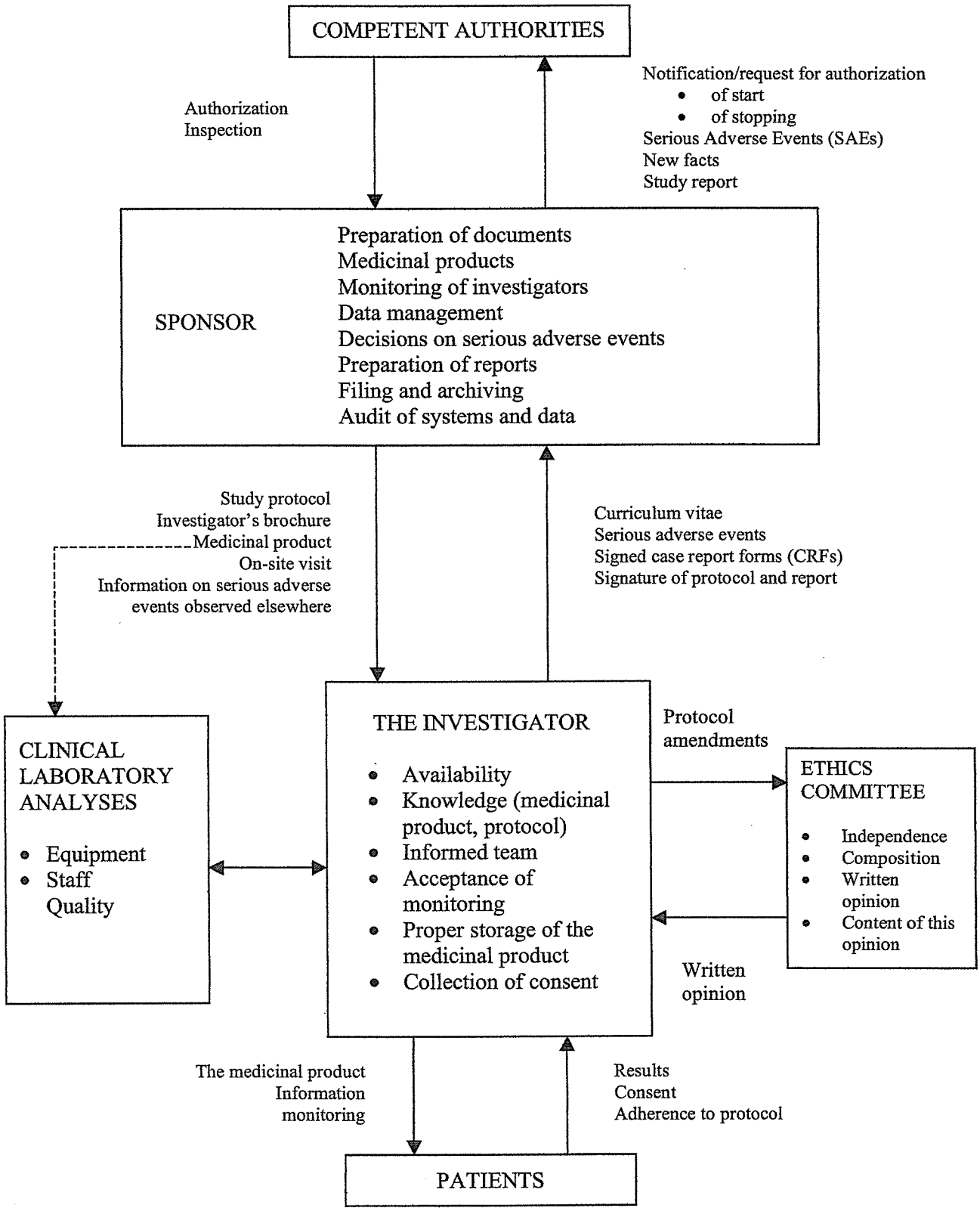

Figure 1. Overall organization of the clinical trial.

the uninterrupted use of their background management. Monitoring the use of the background therapy would be required, however.

Sample size should be sufficient to allow valid statistical analysis and sub-group statistical comparisons, if necessary. It should provide statistical power to support the conclusions of the study. If the conclusions of the study are equivalence of the two treatment groups, then consideration of the power of the study to detect a clinically significant difference is important. Typically, a minimum of 80% power (beta) is required. Levels of disease severity should be recognized and evenly distributed so as not to skew study outcomes toward a possible positive or negative therapeutic response. The ability of subjects to comply with and complete the study should be verified.

A controlled adverse environment (**CAE**) design can be used to control the environment, the subjects' activities, or a combination of both during the clinical trial, thereby providing a stressful environment to exacerbate clinical symptoms and signs of dry eye.[44] Such a stress test is especially valuable in establishing a pharmacological effect in a short period of time. Humidity, temperature, and air-flow are environmental variables that can be monitored and manipulated. Activities can include visual tasks, and the blink rate and tear film stability can be monitored. The trial design should embrace features of a prospective, randomized, masked (to the extent possible), controlled study. Recognition of possible patient adaptation to the conditions of the environmental challenge requires corrective adjustment in data analysis.[45,46] When selecting a patient population based upon the naive response to the challenge environment, such selection may reduce the generalizability of the conclusions of the study to the entire dry eye population.

V. OBSERVATIONS FROM PREVIOUS CLINICAL TRIALS IN DRY EYE

A. Peculiarities of Clinical Trials in Dry Eye

Symptoms and signs have been observed to be closely related in some trials and not in others. Most drug trials have shown a disparity in signs and symptoms.[47-76] There is a prominent apparent placebo or vehicle response in most clinical trials evaluating a topical therapy for dry eye disease.[1] Although placebo effects have been observed in numerous trials that evaluate symptoms, there is also a notable placebo response for objective parameters observed in clinical trials for dry eye. Explanation for this prominent placebo response is not clear, but it may be partially explained by regression to the mean. Most previous clinical trials define entry criteria as a minimal level of severity in outcome parameters. Although this maneuver assures a level of severity to allow demonstration of a measurable effect, it also predisposes to regression to the mean.

The moisturizing and lubricant effect of any topically applied control may also provide an improvement from baseline in manifestations of dry eye disease. Participation in a clinical trial alone has been shown to improve compliance.[3,5] The improvement observed in both control and active trial groups after randomization to a therapy may reflect both subject and observer anticipation and desire for a favorable effect of any proposed therapy. This phenomenon has been termed "expectation of randomization" and may influence the response to either treatment assigned.

B. Evaluation and Outcome Parameters

A review of the literature reveals that Schirmer test, tear film breakup time (**TFBUT**), vital staining scores, and symptoms of discomfort are the most common endpoints used in clinical trials of dry eyes. There was also a wide range of markers used in different trials, depending on the nature of the drug, ie, tear substitutes, anti-inflammatory drugs, and secretagogues. One observation from this review was that the duration of trials was relatively short, varying between 6-8 weeks in trials involving tear substitutes and longer in trials involving anti-inflammatory agents or secretagogues (8-12 weeks with follow-up durations varying between 3-12 months).

Other than the above-mentioned endpoints, trials involving anti-inflammatory agents used tests, biomarkers, and endpoints that included impression cytology (goblet cell numbers, epithelial morphology, and expression of HLA DR, CD3,4,8, 40, Apo2.7, and cytokine profiles). Trials of secretagogues looked at osmolarity, MUC 1, 2, 4 and 5AC mRNA expressions, as well. Apart from the common endpoints mentioned above, trials on devices involving tear retention, such as goggles and punctal plugs, took into consideration the tear clearance rate, tear osmolarity, and tear functional index (**TFI**), as well as standardization of environmental humidity and temperature. These parameters have been used for evaluation of therapies with 1) artificial tears[47-52]; 2) anti-inflammatory agents, including corticosteroids[53,54] and cyclosporine[55-61]; 3) autologous serum [62-66]; secretagogues, including those for aqueous[67-72] and mucin[73-78] stimulation; 4) devices[79-86]; and miscellaneous therapy.[87-88]

C. Suggested Attributes of Clinical Trials in Dry Eye

Inclusion criteria for clinical trials in dry eye should identify, based upon the mechanism of action of the proposed treatment or intervention, a potentially responsive population in which the treatment or intervention is likely to demonstrate efficacy. Inclusion and exclusion criteria should select a specific population that avoids or minimizes confounding variables and regression to the mean. Exclusion criteria are detailed in Section IV above.

A protocol customized to the mechanism of action of the drug or intervention to be tested is most appropriate. Outcome variables should be selected consistent with the mechanism of action of the drug or intervention being tested. The Subcommittee strongly advises inclusion of biomarkers and/or surrogate markers of disease status for future trials, as appropriate with the continued development of technology, but recognizes that validation of such surrogate markers will be needed. For example, increased

osmolarity of the tears is an established marker of dry eye, and there are several possible methods of measurement.

Surrogate markers may be direct or correlative. Direct surrogate markers are those that derive from the same physical or chemical properties as the primary marker, eg, tear conductivity as a measure of tear osmolarity. Correlative surrogate markers are those that correlate with the primary marker but can be produced by other mechanisms as well, eg, a single inflammatory cytokine level as a marker of inflammation.

In dry eye disease, in which variability of a sign or symptom can be greatly influenced by environmental or visual task activities at any given point in time, the measurement of reliable, durable surrogate markers of disease activity should be considered as a valid measure of effectiveness of any given therapy or intervention. The outcome measures should be measurable with adequate accuracy and reproducibility. Measurement of the primary outcome parameter should be accomplished with a well-validated test. This is true for clinical signs of disease and surrogate measures, as well as for symptoms of discomfort and visual disturbance.[89-96] The primary outcome variable may be a symptom or a sign for valid outcome analysis, but regulatory approval may require both in some countries. Symptoms should be graded in a well-defined scoring system, such as the visual analog scale (**VAS**) or with Likert scores.[2,97]

In recognition of the prominence of placebo and vehicle response in clinical trials in dry eye, the Subcommittee made several observations. Because a true placebo has not been found that lacks inherent lubricant effect, consideration of a non-treatment arm could be considered. Although such a design has limitations of possible institutional review board constraints, and given that patients may be prone to intermittent use of over-the-counter lubricants that could confound the outcome, consideration of such a design has merit. In the absence of such a protocol, the Subcommittee recommends consideration of 1) a randomized, masked trial, in which the initiation of treatment is also masked both to investigator and subject, or 2) a withdrawal study, in which all patients initially receive active medication, followed by randomization to vehicle. One benefit of such a design is that all subjects receive active medication at some point in the trial, and this may serve to improve willingness of subjects to enroll in a well-designed trial.

The Subcommittee recommends inclusion of the following outcome parameters:

1. An objective measure of visual function (eg, Functional Visual Acuity);
2. Determination of tear volume and production (eg, Schirmer test or fluorescein dilution test);
3. Determination of tear stability (eg, tear breakup with fluorescein TFBUT or a non-invasive TFBUT device such as videokeratography)[96];
4. Measurement of tear composition (eg, osmolarity, determination of specific protein content, or the measurement of inflammatory mediators in tears);
5. Measurement of ocular surface integrity.

There is consensus that the determination of ocular surface integrity is at this time best performed by staining of the ocular surface with fluorescein and lissamine green or rose bengal (see parameters from the Diagnostic Methodology Subcommittee Report in this issue for appropriate concentrations and use of barrier filters),[98] although the limitations of such evaluation have been documented in previous clinical trials.[58,69,76] A standardized grading system should separately grade corneal and conjunctival staining and record individual area scores, as well as combined area scores, for analysis (see the Diagnostic Methodology Subcommittee Report for appropriate grading system).[98] The grading system should allow for one or two dots of staining in the inferonasal quadrant of the cornea, because such staining may occur in normal subjects.[99-107] Staining of the conjunctival caruncle and semilunar fold should not be counted, as this occurs in a majority of normal subjects.[101]

Other tests that could be used as outcome measures in specific protocols might include impression cytology and flow cytometry (for selected trials, see parameters from the Diagnostic Methodology Subcommittee Report for appropriate method and staining procedure).[98] Technological advances in measurement of tear film stability, measurement of the tear meniscus volume, or measurement of ocular surface protection and epithelial permeability may in the future allow more precise determination of tear function and ocular surface integrity. However, at present, they are not well validated in clinical trials.

Outcome analysis in a multi-factorial disease with several clinical parameters of tear film abnormality, ocular surface damage, and functional impairment may be amenable to composite indices of disease severity. This approach has been utilized in evaluation of rheumatic disease, with consensus development of the American Congress of Rheumatology (ACR) indices (ACR50 and ACR70) that evaluate multiple descriptors of disease severity. Currently, there has been inadequate evaluation of such composite indices in dry eye disease, and validated indices are not available. The committee identifies as a need and an area for future deliberation the development and validation of such indices for evaluation of dry eye disease.

Appropriate and carefully planned statistical analysis is critical in evaluating clinical trial data. The analysis strategy will depend on the primary outcome variable selected for the trial, and it must be chosen prior to the beginning of data collection. The general principle of the intent-to-treat analysis should be adhered to for the primary analysis of data.

VI. FEATURES TO FACILITATE MULTICENTER AND INTERNATIONAL COLLABORATIVE CLINICAL TRIALS

The Subcommittee recommends the development of criteria to be used in multinational venues. Important aspects to consider for such international trials are the use of uniform terminology. This may require that terms are

translated and back-translated for clarity and accuracy. It is necessary to resolve cultural or ethnic connotations or implications in terminology. There should be uniform interpretation of outcome variables with standardized protocols for measurement and recording of data. Testing procedures should be uniform, with use of standardized reagents, standardized protocols, and consistent recording of results. It is necessary to maintain skill levels of data collectors and observers, including certification of investigators and research coordinators and technicians. Attempts should be made to reduce biases related to population differences (race, ethnicity, climatic).

Appendices can be accessed at: wwwtfos (EDITOR: INSERT COMPLETE TFOS ACCESS INFO.)

APPENDIX 1. Outline of a manual of procedures

APPENDIX 2. Guidelines for Good Clinical Practices

APPENDIX 3. Writing the Investigator's Brochure for the tested drug

APPENDIX 4. Using the investigational medicinal product

APPENDIX 5. Adverse events and management issues

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Management and Therapy of Dry Eye Disease:
Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **The members of the Management and Therapy Subcommittee assessed current dry eye therapies. Each member wrote a succinct evidence-based review on an assigned aspect of the topic, and the final report was written after review by and with consensus of all subcommittee members and the entire Dry Eye WorkShop membership. In addition to its own review of the literature, the Subcommittee reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on Dry Eye. The Subcommittee favored the approach taken by the ITF, whose recommended treatments were based on level of disease severity. The recommendations of the Subcommittee are based on a modification of the ITF severity grading scheme, and suggested treatments were chosen from a menu of therapies for which evidence of therapeutic effect had been presented.**

KEYWORDS **DEWS, dry eye disease, Dry Eye WorkShop, management, therapy**

I. INTRODUCTION

This report summarizes the management and therapeutic options for treating dry eye disease. The level of evidence for supporting data from the literature is evaluated according to the modified American Academy of Ophthalmology Preferred Practices guidelines (Table 1).

II. GOALS OF THE MANAGEMENT AND THERAPY SUBCOMMITTEE

Goals of this committee were to identify appropriate therapeutic methods for the management of dry eye disease and recommend a sequence or strategy for their application, based on evidence-based review of the literature.

The quality of the evidence in the literature was graded according to a modification of the scheme used in the American Academy of Ophthalmology Preferred Practice Patterns series. When possible, peer-reviewed full publications, not abstracts, were used. The report was reviewed

Table 1. Evidence grading scheme

Clinical Studies
Level 1. Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches.
Level 2. Evidence obtained from one of the following: a well-designed controlled trial without randomization, a well-designed cohort or case-control analytic study, preferably from one or more center, or a well-designed study accessible to more rigorous statistical analysis.
Level 3. Evidence obtained from one of the following: descriptive studies, case reports, reports of expert committees, expert opinion.
Basic Science Studies
Level 1. Well-performed studies confirming a hypothesis with adequate controls published in a high-impact journal.
Level 2. Preliminary or limited published study.
Level 3. Meeting abstracts or unpublished presentations.

This evidence grading scheme is based on that used in the American Academy of Ophthalmology Preferred Practice Pattern series.

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Management and Therapy Subcommittee members: **Stephen C. Pflugfelder, MD (Chair)**; Gerd Geerling, MD; Shigero Kinoshita, MD; Michael A. Lemp, MD; James McCulley, MD; Daniel Nelson, MD; Gary N. Novack, PhD; Jun Shimazaki, MD; Clive Wilson, PhD.

Proprietary interests of Subcommittee members are disclosed on pages (EDITOR; INSERT PAGE NUMBERS)

Reprints are not available. Articles can be accessed at: (EDITOR: INSERT TFOS WEB SITE INFO)

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OUTLINE

I. Introduction
II. Goals of the Management and Therapy Subcommittee
III. Assessment of current dry eye therapies
  A. Tear supplementation: lubricants
    1. General characteristics and effects
    2. Preservatives
    3. Electrolyte composition
    4. Osmolarity
    5. Viscosity agents
    6. Summary
  B. Tear Retention
    1. Punctal occlusion
      a. Rationale
      b. Types
      c. Clinical studies
      d. Indications and contraindications
      e. Complications
      f. Summary
    2. Moisture chamber spectacles
    3. Contact lenses
  C. Tear stimulation: secretagogues
  D. Biological tear substitutes
    1. Serum
    2. Salivary gland autotransplantation
  E. Anti-inflammatory therapy
    1. Cyclosporine
    2. Corticosteroids
      a. Clinical studies
      b. Basic research
    3. Tetracyclines
      a. Properties of tetracyclines and their derivatives
        1) Antibacterial properties
        2) Anti-inflammatory
        3) Anti-angiogenic properties
      b. Clinical applications of tetracycline
        1) Acne Rosacea
        2) Chronic posterior blepharitis: meibomianitis, meibomian gland dysfunction
        3) Dosage and safety
  F. Essential fatty acids
  G. Environmental strategies
IV. Treatment recommendations
V. Unanswered questions and future directions

by all subcommittee members and by the entire Dry Eye WorkShop membership. Comments and suggested revisions were discussed by the subcommittee members and incorporated into the report where deemed appropriate by consensus.

Table 1. Evidence grading scheme

Clinical Studies
Level 1. Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches.
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Level 3. Evidence obtained from one of the following: descriptive studies, case reports, reports of expert committees, expert opinion.
Basic Science Studies
Level 1. Well-performed studies confirming a hypothesis with adequate controls published in a high-impact journal.
Level 2. Preliminary or limited published study.
Level 3. Meeting abstracts or unpublished presentations.

This evidence grading scheme is based on that used in the American Academy of Ophthalmology Preferred Practice Pattern series.

III. ASSESSMENT OF CURRENT DRY EYE THERAPIES

A. Tear Supplementation: Lubricants

1. General Characteristics and Effects

The term "artificial tears" is a misnomer for most products that identify themselves as such, because they do not mimic the composition of human tears. Most function as lubricants, although some more recent formulations mimic the electrolyte composition of human tears (TheraTears® [Advanced Vision Research, Woburn, MA]).[1,2] The ocular lubricants presently available in the United States are approved based on the US Food and Drug Administration (**FDA**) monograph on over-the-counter (**OTC**) products (21 CFR 349) and are not based on clinical efficacy. The monograph specifies permitted active ingredients (eg, demulcents, emulsifiers, surfactants, and viscosity agents) and concentrations, but gives only limited guidance on inactive additives and solution parameters. Certain inactive ingredients that are used in artificial tears sold in the US (eg, castor oil in Endura™ [Allergan, Inc., Irvine, CA] and guar in Systane® [Alcon, Ft Worth, TX]) are not listed in the monograph.

It is difficult to prove that any ingredient in an ocular lubricant acts as an active agent. If there is an active ingredient, it is the polymeric base or viscosity agent, but this has proved difficult to demonstrate. This is either because it is not possible to detect the effects or differences in clinical trials with presently available clinical tests or because the currently available agents do not have any discernable clinical activity beyond a lubrication effect. Although certain artificial tears have demonstrated more success than others in reducing symptoms of irritation or decreasing ocular surface dye staining in head-to-head comparisons, there have been no large scale, masked, comparative clinical trials

to evaluate the wide variety of ocular lubricants.

What is the clinical effect of ocular lubricants or artificial tears? Do they lubricate, replace missing tear constituents, reduce elevated tear film osmolarity, dilute or wash out inflammatory or inflammation-inducing agents? Do they, in some instances, actually wash out essential substances found in normal human tears? These questions remain to be answered as more sensitive clinical tests become available to detect changes in the ocular surface.

The foremost objectives in caring for patients with dry eye are to improve the patient's ocular comfort and quality of life, and to return the ocular surface and tear film to the normal homeostatic state. Although symptoms can rarely be eliminated, they can often be improved, leading to an improvement in the quality of life. It is more difficult to demonstrate that topical lubricants improve the ocular surface and the tear film abnormalities associated with dry eye. Most clinical studies fail to demonstrate significant correlation between symptoms and clinical test values or between the clinical test values themselves.[3-5] It is not unusual for a dry eye with only mild symptoms to show significant rose bengal staining. Until agents are developed that can restore the ocular surface and tear film to their normal homeostatic state, the symptoms and signs of dry eye will continue.

Ocular lubricants are characterized by hypotonic or isotonic buffered solutions containing electrolytes, surfactants, and various types of viscosity agents. In theory, the ideal artificial lubricant should be preservative-free, contain potassium, bicarbonate, and other electrolytes and have a polymeric system to increase its retention time.[1,6-8] Physical properties should include a neutral to slightly alkaline pH. Osmolarities of artificial tears have been measured to range from about 181 to 354 mOsm/L.[9] The main variables in the formulation of ocular lubricants regard the concentration of and choice of electrolytes, the osmolarity and the type of viscosity/polymeric system, the presence or absence of preservative, and, if present, the type of preservative.

2. Preservatives

The single most critical advance in the treatment of dry eye came with the elimination of preservatives, such as benzalkonium chloride (**BAK**), from OTC lubricants. Because of the risk of contamination of multidose products, most either contain a preservative or employ some mechanism for minimizing contamination. The FDA has required that multidose artificial tears contain preservatives to prevent microbial growth.[10] Preservatives are not required in unit dose vials that are discarded after a single use. The widespread availability of nonpreserved preparations allows patients to administer lubricants more frequently without concern about the toxic effects of preservatives. For patients with moderate-to-severe dry eye, the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants. The ocular surface inflammation associated with dry eye is exacerbated by preserved lubricants; however, nonpreserved solutions are inadequate in themselves to improve the surface inflammation and epithelial pathology seen in dry eye.[11]

Benzalkonium chloride is the most frequently used preservative in topical ophthalmic preparations, as well as in topical lubricants. Its epithelial toxic effects have been well established.[12-17] The toxicity of BAK is related to its concentration, the frequency of dosing, the level or amount of tear secretion, and the severity of the ocular surface disease. In the patient with mild dry eye, BAK-preserved drops are usually well tolerated when used 4-6 times a day or less. In patients with moderate-to-severe dry eye, the potential for BAK toxicity is high, due to decreased tear secretion and decreased turnover.[17] Some patients may be using other topical preparations (eg, glaucoma medications) that contain BAK, increasing their exposure to the toxic effects of BAK. Also, the potential for toxicity exists with patient abuse of other OTC products that contain BAK, such as vasoconstrictors.

BAK can damage the corneal and conjunctival epithelium, affecting cell-to-cell junctions and cell shape and microvilli, eventually leading to cell necrosis with sloughing of 1-2 layers of epithelial cells.[17] Preservative-free formulations are absolutely necessary for patients with severe dry eye with ocular surface disease and impairment of lacrimal gland secretion, or for patients on multiple, preserved topical medications for chronic eye disease. Patients with severe dry eye, greatly reduced tear secretion, and punctal occlusion are at particular risk for preservative toxicity. In such patients, the instilled agent cannot be washed out; if this risk has not been appreciated by the clinician, preserved drops might be used at high frequency.

Another additive used in OTC formulations is disodium (**EDTA**). It augments the preservative efficacy of BAK and other preservatives, but, by itself, it is not a sufficient preservative. Used in some nonpreserved solutions, it may help limit microbial growth in opened unit-dose vials. Although use of EDTA may allow a lower concentration of preservative, EDTA may itself be toxic to the ocular surface epithelium. A study comparing two preservative-free solutions, Hypotears PF® (Novartis Ophthalmics, East Hanover, NJ) containing EDTA and Refresh® (Allergan, Inc., Irvine, CA) without EDTA, showed that both formulations had identical safety profiles and were completely nontoxic to the rabbit corneal epithelium.[18] Other studies found that EDTA-containing preparations increased corneal epithelial permeability.[19,20] The potential exists that patients with severe dry eye will find that EDTA-containing preparations increase irritation.

Nonpreserved, single unit-dose tear substitutes are more costly for the manufacturer to produce, more costly for the patients to purchase, and less convenient to use than bottled ocular lubricants. For these reasons, reclosable unit dose vials (eg, Refresh Free [Allergan Inc., Irvine, CA]; Tears Natural Free® [Alcon, Fort Worth, TX]) were introduced. Less toxic preservatives, such as polyquad (polyquaternium-1), sodium chlorite (Purite®), and sodium perborate were developed to allow the use of multidose bottled lubricants and to avoid the known toxicity of BAK-

containing solutions.[21,22] The "vanishing" preservatives were sodium perborate and sodium purite (TheraTears® [Advanced Vision Research, Woburn, MA], Genteal® [Novartis, East Hanover, NJ], and Refresh Tears® [Allergan Inc., Irvine, CA]).

Sodium chlorite degrades to chloride ions and water upon exposure to UV light after instillation. Sodium perborate is converted to water and oxygen on contact with the tear film. For patients with severe dry eye, even vanishing preservatives may not totally degrade, due to a decrease in tear volume, and may be irritating. Patients prefer bottled preparations for reasons of both cost and ease of use. The ideal lubricant would come in a multidose, easy-to-use bottle that contains a preservative that completely dissipates before reaching the tear film, or is completely nontoxic and nonirritating and maintains absolute sterility with frequent use. One such multi-use, preservative-free product has been introduced to the market (Visine Pure-Tears® [Pfizer, Inc, NJ]).

Ocular ointments and gels are also used in treatment of dry eye. Ointments are formulated with a specific mixture of mineral oil and petrolatum. Some contain lanolin, which can be irritating to the eye and delay corneal wound healing.[23] Individuals with sensitivity to wool may also be sensitive to lanolin.[23] Some ointments contain parabens as preservatives, and these ointments are not well tolerated by patients with severe dry eye. In general, ointments do not support bacterial growth and, therefore, do not require preservatives. Gels containing high molecular weight cross-linked polymers of acrylic acid (carbomers) have longer retention times than artificial tear solutions, but have less visual blurring effect than petrolatum ointments.

3. Electrolyte Composition

Solutions containing electrolytes and or ions have been shown to be beneficial in treating ocular surface damage due to dry eye.[1,6,20,24,25] To date, potassium and bicarbonate seem to be the most critical. Potassium is important to maintain corneal thickness.[7] In a dry-eye rabbit model, a hypotonic tear-matched electrolyte solution (TheraTears® [Advanced Vision Research, Woburn, MA]) increased conjunctival goblet cell density and corneal glycogen content, and reduced tear osmolarity and rose bengal staining after 2 weeks of treatment.[25] The restoration of conjunctival goblet cells seen in the dry-eye rabbit model has been corroborated in a patients with dry eye after LASIK.[26]

Bicarbonate-containing solutions promote the recovery of epithelial barrier function in damaged corneal epithelium and aid in maintaining normal epithelial ultrastructure. They may also be important for maintaining the mucin layer of the tear film.[6] Ocular lubricants are available that mimic the electrolyte composition of human tears, eg, TheraTears® (Advanced Vision Research, Woburn, MA) and BION Tears® (Alcon, Fort Worth, TX).[1,2] These also contain bicarbonate, which is critical for forming and maintaining the protective mucin gel in the stomach.[27] Bicarbonate may play a similar role for gel-forming mucins on the ocular surface. Because bicarbonate is converted to carbon dioxide when in contact with air and can diffuse through the plastic unit dose vials, foil packaging of the plastic vials is required to maintain stability.

4. Osmolarity

Tears of patients with dry eye have a higher tear film osmolarity (crystalloid osmolarity) than do those of normal patients.[28,29] Elevated tear film osmolarity causes morphological and biochemical changes to the corneal and conjunctival epithelium[18,30] and is pro-inflammatory.[31] This knowledge influenced the development of hypo-osmotic artificial tears such as Hypotears® (230 mOsm/L [Novartis Ophthalmics, East Hanover, NJ]) and subsequently TheraTears® (181 mOsm/L [Advance Vision Research, Woburn, MA]).[32]

Colloidal osmolality is another factor that varies in artificial tear formulations. While crystalloid osmolarity is related to the presence of ions, colloidal osmolality is dependent largely on macromolecule content. Colloidal osmolarity, also known as *oncotic pressure*, is involved in the control of water transport in tissues. Differences in colloidal osmolality affect the net water flow across membranes, and water flow is eliminated by applying hydrostatic pressure to the downside of the water flow. The magnitude of this osmotic pressure is determined by osmolality differences on the two sides of the membrane. Epithelial cells swell due to damage to their cellular membranes or due to a dysfunction in the pumping mechanism. Following the addition of a fluid with a high colloidal osmolality to the damaged cell surface, deturgescence occurs, leading to a return of normal cell physiology. Theoretically, an artificial tear formulation with a high colloidal osmolality may be of value. Holly and Esquivel evaluated many different artificial tear formulations and showed that Hypotears® (Novartis Ophthalmics, East Hanover, NJ) had the highest colloidal osmolality of all of the formulations tested.[33] Formulations with higher colloidal osmolality have since been marketed (Dwelle® [Dry Eye Company, Silverdale, WA]).

Protection against the adverse effects of increased osmolarity (osmoprotection) has led to development of OTC drops incorporating compatible solutes (such as glycerin, erythritol, and levocarnitine (Optive® [Allergan Inc., Irvine, CA]). It is thought that the compatible solutes distribute between the tears and the intracellular fluids to protect against potential cellular damage from hyperosmolar tears.[34]

5. Viscosity Agents

The stability of the tear film depends on the chemical-physical characteristics of that film interacting with the conjunctival and corneal epithelium via the membrane-spanning mucins (ie, MUC-16 and MUC-4). In the classical three-layered tear film model, the mucin layer is usually thought of as a surfactant or wetting agent, acting to lower the surface tension of the relatively hydrophobic ocular surface, rendering the corneal and conjunctival cells "wettable."[33] Currently, the tear film is probably best described

as a hydrated, mucin gel whose mucin concentration decreases with distance from the epithelial cell surface. It may have a protective role similar to that of mucin in the stomach.[35] It may also serve as a "sink" or storage vehicle for substances secreted by the main and accessory lacrimal glands and the ocular surface cells. This may explain why most of the available water-containing lubricants are only minimally effective in restoring the normal homeostasis of the ocular surface. In addition to washing away and diluting out irritating or toxic substances in the tear film, artificial lubricants hydrate gel-forming mucin. While some patients with dry eye have decreased aqueous lacrimal gland secretion, alterations or deficiencies involving mucin also cause dry eye.

Macromolecular complexes added to artificial lubricants act as viscosity agents. The addition of a viscosity agent increases residence time, providing a longer interval of patient comfort. For example, when a viscous, anionic charged carboxymethyl-cellulose (CMC, 100,000 mw) solution was compared with a neutral hydroxymethylcellulose (HPMC) solution, CMC was shown to have a significantly slower rate of clearance from the eye.[36] Viscous agents in active drug formulations may also prolong ocular surface contact, increasing the duration of action and penetration of the drug.

Viscous agents may also protect the ocular surface epithelium. It is known that rose bengal stains abnormal corneal and conjunctival epithelial cells expressing an altered mucin glycocalyx.[37] Agents such as hydroxymethycellulose (**HMC**), which decrease rose bengal staining in dry eye subjects,[38] may either "coat and protect" the surface epithelium or help restore the protective effect of mucins.

In the US, carboxymethyl cellulose is the most commonly used polymeric viscosity agent (IRI Market Share Data, Chicago, IL), typically in concentrations from 0.25% to 1%, with differences in molecular weight also contributing to final product viscosity. Carboxymethyl cellulose has been found to bind to and be retained by human epithelial cells.[39] Other viscosity agents included in the FDA monograph (in various concentrations) include polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose, hydroxypropyl cellulose, and carboxymethyl cellulose.

The blurring of vision and esthetic disadvantages of caking and drying on eyelashes are drawbacks of highly viscous agents that patients with mild to moderate dry eye will not tolerate. Lower molecular-weight viscous agents help to minimize these problems. Because patient compliance, comfort, and convenience are important considerations, a range of tear substitute formulations with varying viscosities are needed.

Hydroxypropyl-guar (HP-guar) has been used as a gelling agent in a solution containing glycol 400 and propylene glycol (Systane®, Alcon, Fort Worth, TX). It has been suggested that HP-guar preferentially binds to the more hydrophobic, desiccated or damaged areas of the surface epithelial cells, providing temporary protection for these cells.[40,41] Several commercial preparations containing oil in the form of castor oil (Endura™ [Allergan Inc., Irvine, CA]) or mineral oil (Soothe® [Bausch & Lomb, Rochester, NY]) are purported to aid in restoring or increasing the lipid layer of the tear film.[42,43] Hyaluronic acid is a viscosity agent that has been investigated for years as an "active" compound added to tear substitute formulations for the treatment of dry eye. Hyaluronic acid (0.2%) has significantly longer ocular surface residence times than 0.3 percent HPMC or 1.4 percent polyvinyl alcohol.[44] Some clinical studies reported improvement in [44-48] dry eye in patients treated with sodium hyaluronate-containing solutions compared to other lubricant solutions, whereas others did not.[48] Although lubricant preparations containing sodium hyaluronate have not been approved for use in the US, they are frequently used in some countries.

6. Summary

Although many topical lubricants, with various viscosity agents, may improve symptoms and objective findings, there is no evidence that any agent is superior to another. Most clinical trials involving topical lubricant preparations will document some improvement (but not resolution) of subjective symptoms and improvement in some objective parameters.[4] However, the improvements noted are not necessarily any better than those seen with the vehicle or other nonpreserved artificial lubricants. The elimination of preservatives and the development of newer, less toxic preservatives have made ocular lubricants better tolerated by dry eye patients. However, ocular lubricants, which have been shown to provide some protection of the ocular surface epithelium and some improvement in patient symptoms and objective findings, have not been demonstrated in controlled clinical trials to be sufficient to resolve the ocular surface disorder and inflammation seen in most dry eye sufferers.

B. Tear Retention

1. Punctal Occlusion

a. Rationale

While the concept of permanently occluding the lacrimal puncta with cautery to treat dry eye extends back 70 years,[49] and, although the first dissolvable implants were used 45 years ago,[50] the modern era of punctal plug use began in 1975 with the report by Freeman.[51] Freeman described the use of a dumbbell-shaped silicone plug, which rests on the opening of the punctum and extends into the canaliculus. His report established a concept of punctal occlusion, which opened the field for development of a variety of removable, long-lasting plugs to retard tear clearance in an attempt to treat the ocular surface of patients with deficient aqueous tear production. The Freeman style plug remains the prototype for most styles of punctal plugs.

b. Types

Punctal plugs are divided into two main types: absorbable and nonabsorbable. The former are made of collagen or polymers and last for variable periods of time (3 days to 6 months). The latter nonabsorbable "permanent" plugs

include the Freeman style, which consists of a surface collar resting on the punctal opening, a neck, and a wider base. In contrast, the Herrick plug (Lacrimedics [Eastsound,WA]) is shaped like a golf tee and is designed to reside within the canaliculus. It is blue for visualization; other variations are radiopaque. A newly designed cylindrical Smartplug™ (Medennium Inc [Irvine, CA]) expands and increases in diameter in situ following insertion into the canaliculus due to thermodynamic properties of its hydrophilic acrylic composition.

c. Clinical Studies

A variety of clinical studies evaluating the efficacy of punctal plugs have been reported.[52-56] These series generally fall into Level II evidence. Their use has been associated with objective and subjective improvement in patients with both Sjogren and non-Sjogren aqueous tear deficient dry eye, filamentary keratitis, contact lens intolerance, Stevens-Johnson disease, severe trachoma, neurotrophic keratopathy, post-penetrating keratoplasty, diabetic keratopathy, and post-photorefractive keratectomy or laser in situ keratomileusis. Several studies have been performed to evaluate the effects of punctal plugs on the efficacy of glaucoma medications in reducing intraocular pressure, and these studies have reported conflicting results.[57,58] Beneficial outcome in dry eye symptoms has been reported in 74-86% of patients treated with punctal plugs. Objective indices of improvement reported with the use of punctal plugs include improved corneal staining, prolonged tear film breakup time (**TFBUT**), decrease in tear osmolarity, and increase in goblet cell density. Overall, the clinical utility of punctal plugs in the management of dry eye disease has been well documented.

d. Indications and Contraindications

In a recent review on punctal plugs, it was reported that in a major eye clinic, punctal plugs are considered indicated in patients who are symptomatic of dry eyes, have a Schirmer test (with anesthesia) result less than 5 mm at 5 minutes, and show evidence of ocular surface dye staining.[56]

Contraindications to the use of punctal plugs include allergy to the materials used in the plugs to be implanted, punctal ectropion, and pre-existing nasolacrimal duct obstruction, which would, presumably, negate the need for punctal occlusion. It has been suggested that plugs may be contraindicated in dry eye patients with clinical ocular surface inflammation, because occlusion of tear outflow would prolong contact of the abnormal tears containing proinflammatory cytokines with the ocular surface. Treatment of the ocular surface inflammation prior to plug insertion has been recommended. Acute or chronic infection of the lacrimal canaliculus or lacrimal sac is also a contraindication to use of a plug.

e. Complications

The most common complication of punctal plugs is spontaneous plug extrusion, which is particularly common with the Freeman-style plugs. Over time, an extrusion rate of 50% has been reported, but many of these extrusions took place after extensive periods of plug residence. Most extrusions are of small consequence, except for inconvenience and expense. More troublesome complications include internal migration of a plug, biofilm formation and infection,[59] and pyogenic granuloma formation. Removal of migrated canalicular plugs can be difficult and may require surgery to the nasolacrimal duct system.[60,61]

f. Summary

The extensive literature on the use of punctal plugs in the management of dry eye disease has documented their utility. Several recent reports, however, have suggested that absorption of tears by the nasolacrimal ducts into surrounding tissues and blood vessels may provide a feedback mechanism to the lacrimal gland regulating tear production.[62] In one study, placement of punctal plugs in patients with normal tear production caused a significant decrease in tear production for up to 2 weeks after plug insertion.[63] This cautionary note should be considered when deciding whether to incorporate punctal occlusion into a dry eye disease management plan.

2. Moisture Chamber Spectacles

The wearing of moisture-conserving spectacles has for many years been advocated to alleviate ocular discomfort associated with dry eye. However, the level of evidence supporting its efficacy for dry eye treatment has been relatively limited. Tsubota et al, using a sensitive moisture sensor, reported an increase in periocular humidity in subjects wearing such spectacles.[64] Addition of side panels to the spectacles was shown to further increase the humidity.[65] The clinical efficacy of moisture chamber spectacles has been reported in case reports.[66,67] Kurihashi proposed a related treatment for dry eye patients, in the form of a wet gauze eye mask.[68] Conversely, Nichols et al recently reported in their epidemiologic study that spectacle wearers were twice as likely as emmetropes to report dry eye disease.[69] The reason for this observation was not explained.

There have been several reports with relatively high level of evidence describing the relationship between environmental humidity and dry eye. Korb et al reported that increases in periocular humidity caused a significant increase in thickness of the tear film lipid layer.[70] Dry eye subjects wearing spectacles showed significantly longer interblink intervals than those who did not wear spectacles, and duration of blink (blinking time) was significantly longer in the latter subjects.[70] Instillation of artificial tears caused a significant increase in the interblink interval and a decrease in the blink rate.[71] Maruyama et al reported that dry eye symptoms worsened in soft contact lens wearers when environmental humidity decreased.[72]

3. Contact Lenses

Contact lenses may help to protect and hydrate the corneal surface in severe dry eye conditions. Several differ-

ent contact lens materials and designs have been evaluated, including silicone rubber lenses and gas permeable scleral-bearing hard contact lenses with or without fenestration.[73-77] Improved visual acuity and comfort, decreased corneal epitheliopathy, and healing of persistent corneal epithelial defects have been reported.[73-77] Highly oxygen-permeable materials enable overnight wear in appropriate circumstances.[75] There is a small risk of corneal vascularization and possible corneal infection associated with the use of contact lenses by dry eye patients.

C. Tear Stimulation: Secretogogues

Several potential topical pharmacologic agents may stimulate aqueous secretion, mucous secretion, or both. The agents currently under investigation by pharmaceutical companies are diquafosol (one of the P2Y2 receptor agonists), rebamipide, gefarnate, ecabet sodium (mucous secretion stimulants), and 15(S)-HETE (MUC1 stimulant). Among them, a diquafosol eye drop has been favorably evaluated in clinical trials. 2% diquafosol (INS365, DE-089 [Santen, Osaka, Japan]; Inspire [Durham, NC]) proved to be effective in the treatment of dry eye in a randomized, double-masked trial in humans to reduce ocular surface staining.[78] A similar study demonstrated the ocular safety and tolerability of diquafosol in a double-masked, placebo-controlled, randomized study.[79] This agent is capable of stimulating both aqueous and mucous secretion in animals and humans.[80-83] Beneficial effects on corneal epithelial barrier function, as well as increased tear secretion, has been demonstrated in the rat dry eye model.[84] Diquafosol also has been shown to stimulate mucin release from goblet cells in a rabbit dry eye model.[85,86]

The effects of rebamipide (OPC-12759 [Otsuka, Rockville, MD]; Novartis [Basel, Switzerland]) have been evaluated in human clinical trials. In animal studies, rebamipide increased the mucin-like substances on the ocular surface of N-acetylcysteine-treated rabbit eyes.[87] It also had hydroxyl radical scavenging effects on UVB-induced corneal damage in mice.[88]

Ecabet sodium (Senju [Osaka, Japan]; ISTA [Irvine, CA]) is being evaluated in clinical trials internationally, but only limited results have yet been published. A single instillation of ecabet sodium ophthalmic solution elicited a statistically significant increase in tear mucin in dry eye patients.[89] Gefarnate (Santen [Osaka, Japan]) has been evaluated in animal studies. Gefarnate promoted mucin production after conjunctival injury in monkeys.[90] Gefarnate increased PAS-positive cell density in rabbit conjunctiva and stimulated mucin-like glycoprotein stimulation from rat cultured corneal epithelium.[91,92] An in vivo rabbit experiment showed a similar result.[93,94]

The agent 15(S)-HETE, a unique molecule, can stimulate MUC1 mucin expression on ocular surface epithelium.[95]15(S)-HETE protected the cornea in a rabbit model of desiccation-induced injury, probably because of mucin secretion.[96] It has been shown to have beneficial effects on secretion of mucin-like glycoprotein by the rabbit corneal epithelium.[97] Other laboratory studies confirm the stimulatory effect of 15(S)-HETE.[98-101] Some of these agents may become useful clinical therapeutic modalities in the near future.

Two orally administered cholinergic agonists, pilocarpine and cevilemine, have been evaluated in clinical trials for treatment of Sjogren syndrome associated keratoconjunctivitis sicca (**KCS**). Patients who were treated with pilocarpine at a dose of 5 mg QID experienced a significantly greater overall improvement than placebo-treated patients in "ocular problems" in their ability to focus their eyes during reading, and in symptoms of blurred vision compared with placebo-treated patients.[102] The most commonly reported side effect from this medication was excessive sweating, which occurred in over 40% of patients. Two percent of the patients taking pilocarpine withdrew from the study because of drug-related side effects. Other studies have reported efficacy of pilocarpine for ocular signs and symptoms of Sjogren syndrome KCS,[103-105] including an increase in conjunctival goblet cell density after 1and 2 months of therapy.[106]

Cevilemine is another oral cholinergic agonist that was found to significantly improve symptoms of dryness and aqueous tear production and ocular surface disease compared to placebo when taken in doses of 15 or 30 mg TID.[107,108] This agent may have fewer adverse systemic side effects than oral pilocarpine.

D. Biological Tear Substitutes

Naturally occurring biological, ie, nonpharmaceutical fluids, can be used to substitute for natural tears. The use of serum or saliva for this purpose has been reported in humans. They are usually unpreserved. When of autologous origin, they lack antigenicity and contain various epitheliotrophic factors, such as growth factors, neurotrophins, vitamins, immunoglobulins, and extracellular matrix proteins involved in ocular surface maintenance. Biological tear substitutes maintain the morphology and support the proliferation of primary human corneal epithelial cells better than pharmaceutical tear substitutes.[109] However, despite biomechanical and biochemical similarities, relevant compositional differences compared with normal tears exist and are of clinical relevance.[110] Additional practical problems concern sterility and stability, and a labor-intensive production process or a surgical procedure (saliva) is required to provide the natural tear substitute to the ocular surface.

1. Serum

Serum is the fluid component of full blood that remains after clotting. Its topical use for ocular surface disease was much stimulated by Tsubota's prolific work in the late 1990s.[111] The practicalities and published evidence of autologous serum application were recently reviewed.[112] The use of blood and its components as a pharmaceutical preparation in many countries is restricted by specific national laws. To produce serum eye drops and to use