

TearLab™ Research Guide Tips and Recommendations

The following tips and recommendations are for the use of the TearLab Osmolarity System in your research or clinical study for Dry Eye Disease (DED). These recommendations address issues in study design that will give your trial the best chance of success.

If you require additional assistance, we are happy to provide input and recommendation on your study design and protocol. If necessary, we are willing to do this under confidentiality agreement.

1. Daily Quality Control (QC)

On every day of subject testing, TearLab Control Solutions should be tested to confirm that the TearLab Osmolarity System is functioning properly. Always record the test results in a QC Log. In this way, you will be confident that the osmolarity data in your study is correct, even when the study data is presenting unexpected or unusual results. TearLab control solutions are assayed against and traceable to international reference standards, and are the only control solutions that should be used with the TearLab Osmolarity System. Also, since TearLab control solutions are traceable to reference standards, they should not be diluted or titrated. Please note that TearLab control solutions are assayed against the TearLab impedance osmolarity method and will not read the same value if tested on other types of osmometers. TearLab can supply you with a QC Log template and QC procedures for your study upon request.

2. Test Two Eyes

Always test both eyes in every study. Although dry eye is a bilateral disease, it is not symmetrical. It is recognized that biological variability between the left and right eye is a hallmark of dry eye disease and testing only one eye will compromise your study results. TearLab has developed testing techniques and methods of data analysis to mitigate biological variability and will be happy to share our recommendations with you based on your study protocol and goals.

3. Inclusion / Exclusion Criteria

Because there are many etiologies and types of dry eye disease, inclusion criteria based on traditional clinical tests may fail to properly classify the mild/moderate subjects in your study. Most important, signs and symptoms *do not progress in concert nor do they correlate with each other*. For example, someone with a low tear breakup time may not have corneal staining. Therefore, inclusion criteria based on a series of thresholds (i.e., TBUT < 7 seconds AND Schirmer's test < 5 mm AND staining > grade 1, etc.) may result in dry eye subjects being recruited into your normal subject cohort .

Data demonstrate that the most reliable, linear indication of disease severity is a repeated measurement of tear film osmolarity. It is well known that as severity increases, the tear film becomes progressively unstable. As such, the osmolarity of normal subjects does not vary – resulting in a longitudinal standard deviation of 5 mOsm/L or less. Subjects with mild/moderate dry eye are consistently more variable, with deviations around 7-12 mOsm/L, while severe subjects are unstable, with standard deviations over time of 13-20 mOsm/L or higher. This increase in variability is thought to be due to the inherent instability of the tear film in dry eye disease and the role of compensatory mechanisms e.g. reflex tearing, blinking, squinting etc. which drive tear osmolarity down transiently and asymmetrically.

If you test both eyes and take the higher number - which more accurately reflects the disease process - using a cut-off value of 308 mOsm/L, you will correctly identify patients with dry eye disease 86% of the time. While not recommended for clinical practice due to cost and convenience, one-time triplicate bilateral osmolarity measurements will correctly identifying dry eye subjects for inclusion in research studies nearly 100% of the time, despite the above-mentioned variability.

When selecting patients for your study, it may be important to eliminate subjects presenting with intermittent disease. Because dry eye disease is difficult to diagnose in its early stages, many of these subjects may have a different ocular surface disease altogether (allergy, etc.) and should be excluded from both normal and dry eye cohorts. Osmolarity as an inclusion/exclusion criterion can help to identify subjects with concomitant disease or those that do not have a clear case of dry eye.

4. Testing Order

Most studies incorporate multiple dry eye tests and examinations in the study method. It is important that the TearLab test (as the least invasive test) be performed first, before any test that may destabilize or adulterate the tear film. This includes all invasive tests such as Schirmer's, staining, TBUT, etc., including slit lamp exams that may induce reflex tearing from a bright light.

5. Eye Drops and Medications

If the subject is using eye drops or topical medication, either as part of the study or on their own, *it is essential that the subject be instructed NOT to use eye drops within 2 hours prior to the TearLab test.* Eye drops or medications instilled into the eye within 2 hours may contaminate the basal tear film and provide inaccurate test results. It is recommended that the time the last eye drop or topical medication was used by the patient be recorded on the case report form, together with the osmolarity test result, in order to better control for this factor. If the study goal is to determine clearance rates for ocular medication/eye drops, it is recommended that you contact TearLab

for input and suggestions on how to best implement testing into your study plan.

6. Symptom Questionnaire

If your study intends to track symptoms, TearLab has experience with several types of symptom questionnaires, and we will be happy to make recommendations based on your study goals. Usually, it is important to consider a symptom questionnaire that includes a measure of relative change in symptoms following the onset of therapy, *e.g.*, visual analog scales or the “Symptom Assessment iN Dry Eye” (SANDE) questionnaire. If you choose to use the “Ocular Surface Disease Index” (OSDI) scale, new recommendations for severity grading and significant change are available.

7. Contact Lens Studies

Contact lens wear will affect tear osmolarity differently in normal and dry eye subjects. Therefore it may be important to correctly identify your subjects as normal or dry eye prior to recruitment and without the effect of contact lens wear. Also, the insertion and removal of the contact lens may destabilize the tear film; so allow 10-15 minutes to test the tear film before insertion or after removal of the lens from the eye. Also, *to measure the effect of lens wear, it is recommended that tear osmolarity be tested with the lens in the eye*, as tear film may return to normal levels over time after removal of the lens. Confounding variables should be controlled in a contact lens study, including type of lens, care of the lens, use of re-wetting drops and length of wear. Daily logs kept by the subject may be useful in this regard.

8. Treatment Logs

If your study requires use of eye drops, medications or nutritional supplements, it is recommended that the study subject keep a daily log documenting usage and include this log in the data analysis. This will also encourage compliance, and allow you to identify non-compliance during the study.

9. Data Analysis

The multifactorial nature of dry eye disease makes statistical analyses non-trivial. TearLab will be happy to provide recommendations on data analysis and in certain circumstances, assist with the effort.

10. Training

Although TearLab is extremely simple to operate, it is important that the operation of the device follows manufacturer recommendations in order to ensure accurate and precise results. TearLab Corporation and its authorized representatives are the best source to provide training, including training outlines, videos and train-the-trainer support for your studies. Please confer with us prior to the beginning of your study to discuss the most effective way to educate your study sites.

TearLab Corporation - Your Research Partner

We will provide the following services to our research customers at no cost:

- Study design, protocol review and recommendation, specifically relative to the measurement of tear film osmolarity
- TearLab Osmolarity System training support and aids, including training videos, quality control procedures and logs
- Data analysis recommendation and review

We also have in house CRO services that we can make available for your trial along with the ability to provide complete statistical analysis all for a fraction of the normal research cost.

If you are interested in discussing your research study or have additional questions regarding the use of the TearLab Osmolarity System, please contact:

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