WHITE PAPER

Dry eye syndrome clinical trials: Key design considerations for consistent, interpretable data



A KEY QUESTION

How can sponsors design scientifically rigorous, operationally feasible dry eye syndrome studies that generate consistent, interpretable data?

KEYWORDS Dry Eye Syndrome (DES), Clinical Trial Design, Ophthalmology Clinical Trials, Patient Selection, Diagnostic Assessments, Patient Compliance, Endpoint Strategy

Authors
Naidan Luo, MD, PhD, Senior Medical Director, Fortrea
David D. Hoelscher, MD, Senior Medical Director, Fortrea
Laurentiu Gutiu, MD, Executive Medical Director, TA Lead Neuroscience and Opthalmology, Fortrea

Executive summary

Dry eye syndrome (DES) presents a complex clinical development environment.[1,2] Symptoms and clinical signs can vary considerably between patients,[1,2] while differences in diagnostic approaches, vehicle response, concomitant treatments and trial design can introduce additional variability.[1,3,4]

For sponsors, generating consistent and interpretable data requires connected decisions across the trial. The study population must be clearly characterized, endpoints must align with the intended treatment effect and assessment procedures must be standardized across patients, visits and sites. Control interventions, background treatments and relevant baseline differences should also be considered during protocol development.

Drawing on experience from a recent DES clinical trial conducted by a biotechnology company in China, with Fortrea supporting trial execution, this paper explores how these considerations can be applied in practice. It examines patient selection, endpoint strategy, concomitant medication management, ophthalmic assessment procedures and statistical design, highlighting how early planning can reduce avoidable variability and support clinically meaningful data.

Key takeaways

- **Define the study population carefully.** Combining symptom measures, objective clinical findings and, where relevant, disease duration can help establish a consistently characterized population
- **Align endpoints with the clinical question.** Objective assessments and patient-reported measures capture different aspects of DES and should be considered in relation to the intended effect of the investigational treatment
- **Standardize endpoint execution.** Personnel, procedures, timing, testing environment, supplies and assessment sequence can all influence measurement consistency
- **Consider vehicle response and concomitant treatments prospectively.** Control interventions, artificial tears, prohibited medications and washout requirements can influence how treatment effects are interpreted
- **Connect clinical and statistical design.** Baseline symptom and clinical measures can inform stratification and statistical analysis as well as eligibility
- **Plan operational decisions before study initiation.** Defining assessment procedures, handling of out-of-range measurements and other practical requirements in advance can reduce site-level variability during study conduct

Why dry eye syndrome trials are challenging

DES is a complex condition in which symptoms and clinical signs can vary substantially between patients.[1,2] This variability, together with differences in how DES is assessed, creates challenges for clinical development teams seeking to distinguish treatment effects from changes that may arise from the study population, control intervention, concomitant therapies or assessment procedures.[1,3,4]

The growing interest in DES research makes these considerations increasingly relevant. A primary analysis of industry-sponsored DES trials provides insight into the dry eye clinical trial landscape and evolving dry eye pipeline, identifying 80 studies across Phases I through III/IV, spanning a broad range of therapeutic approaches.[5] The analysis also showed that studies commonly incorporate combinations of clinical response measures, symptom assessments and patient-reported outcomes, alongside objective assessments such as ocular surface staining and Schirmer testing.[5]

The analysis also identified substantial activity in Asia and North America, particularly the United States and China, while the therapeutic approaches under investigation reflected a diverse range of mechanisms of action, including inflammatory, hormonal, neurological, endocrine and immune-related pathways.[5]

This diversity in therapeutic approaches and assessment methods highlights the importance of aligning trial design with the clinical question and intended treatment effect. Different measures capture different aspects of DES,[1,2] while differences in the enrolled population and assessment methodology can affect the resulting data.[1,3] For sponsors, this means considering patient selection, endpoint strategy, control and concomitant treatment and assessment execution as connected elements of trial design.

The following sections examine these considerations in more detail, drawing on practical experience from a recent DES clinical trial conducted by a biotechnology company in China, with Fortrea supporting trial execution.

Selecting the right patients can reduce avoidable variability

Patient selection is one of the first opportunities to manage variability within a DES clinical trial. The heterogeneity of symptoms and clinical signs means that seemingly small differences in the characteristics of enrolled patients can contribute to differences in study outcomes.[1,4,6]

Dry eye enrollment criteria should therefore reflect the clinical question and intended study population, while incorporating measures that characterize both symptom burden and clinical disease. Depending on the study objectives, this may include patient-reported symptoms, objective clinical findings and disease duration.

No single measure necessarily captures all the characteristics relevant to the intended study population.[3,6,7] Combining complementary measures can provide a more comprehensive and consistent framework for identifying patients with the disease characteristics relevant to the trial.[6]

In the recent DES trial, eligibility criteria incorporated Eye Dryness Score (EDS), corneal fluorescein staining (CFS), Schirmer test results, slit-lamp findings and symptom duration. This approach illustrates how subjective and objective measures can be combined to establish a more consistently characterized study population.

Eligibility criteria should also accommodate clinical findings that may require individual assessment. Findings such as corneal epithelial defects may require consideration of their clinical significance, relationship to DES and potential impact on patient safety or evaluation of the investigational treatment.

Clearly defined criteria provide a consistent framework for screening, while appropriate clinical judgment allows individual findings to be considered in context.[6]

Patient selection also connects with decisions made later in the trial. Baseline measures can provide information about the characteristics of a population enrolled and may identify prognostic factors that are relevant to randomization strategies, assessment of treatment-group comparability and subsequent statistical analysis.[6,8,9]

This creates an important link between eligibility criteria and statistical design: The characteristics used to define the study population may also inform how relevant baseline variability is addressed.

For sponsors, the objective is therefore not simply to recruit enough patients, but to establish a sufficiently well-characterized population to address the clinical question while recognizing and accounting for relevant variability. Careful patient selection cannot eliminate the inherent variability of DES, but it can provide a clearly defined starting point from which treatment effects can be assessed and interpreted.

Endpoint strategy needs to capture both the patient's experience and measurable clinical change

Selecting appropriate clinical endpoints is central to the design of a DES clinical trial. No single assessment necessarily captures the full patient experience or all of the clinical changes associated with DES.[1,6,7]

Objective and patient-reported measures provide different perspectives. Schirmer testing can provide information about tear production, while tear film break-up time (TBUT) provides information about tear film stability and CFS can assess ocular surface damage and changes in corneal epithelial integrity.[10] Patient-reported measures such as Visual Analog Scales (VAS), the Ocular Surface Disease Index (OSDI) and EDS provide information about symptoms and the patient's experience of disease.[10,11]

These measures are not interchangeable.[1] They address different aspects of DES and may therefore provide complementary information about whether an intervention is affecting clinical features of the disease and whether those changes are reflected in the patient's experience.[1,6]

Selecting an endpoint is only part of the design process. The way an endpoint is assessed can also influence the consistency and interpretation of the resulting data.

Factors such as personnel, procedures, timing, assessment sequence and environmental conditions can contribute to the variability in measurements, particularly for ophthalmic assessments that depend on standardized examination techniques.[6,12] These considerations should therefore be addressed during protocol development rather than left entirely to site-level implementation.

The recent DES trial illustrates this principle through its approach to Schirmer testing and other ophthalmic assessments. The study established defined procedures for assessment timing, sequence and test execution, demonstrating how endpoint methodology can be incorporated into the broader trial design.

Standardization should extend beyond defining what is being measured to specifying how, when and under what conditions it is measured.

For multicenter DES trials, sponsors should consider whether assessment personnel can be trained consistently, whether procedures and timing can be clearly defined and whether environmental or equipment-related factors could influence measurements. The protocol should also anticipate how unusual or out-of-range results will be handled.

The broader principle is that endpoint selection and endpoint execution should be considered together. A clinically relevant endpoint can only provide interpretable data if it can also be measured consistently across patients, visits and sites.



Vehicle response and concomitant therapies need to be considered in trial design

Once the study population and endpoint strategy have been defined, the treatment effect also needs to be interpreted in the context of the control intervention and other therapies used during the trial.[3]

This is particularly relevant in DES, where the vehicle may influence symptoms or clinical signs, while patients may routinely use symptomatic treatments such as artificial tears.[2,3,4] Decisions about the control group, washout requirements and permitted concomitant therapies can therefore influence the conditions under which treatment effects are observed.[4]

The vehicle used as a comparator is generally designed to maintain masking while remaining sufficiently similar to the active treatment.[3,4,6] However, changes observed in the control group may reflect more than the absence of active treatment. The study therefore needs to distinguish the effect of the investigational treatment from changes that may occur under control conditions.[13,14]

Depending on the treatment and study objectives, approaches such as a vehicle run-in or withdrawal design may be considered.[4,6] A run-in can help characterize response to the control intervention before randomization, while withdrawal designs require consideration of how long treatment effects may persist after discontinuation and how this relates to the mechanism of action of the investigational treatment.[4,6]

Artificial tears are a particularly relevant consideration because they may already form part of a patient's routine management of DES.[2,3,4]

In the recent Fortrea supported DES trial, artificial tears were permitted under defined conditions and their use was considered in the study analysis. Experience from completed Phase III trials in the United States using the same protocol also included artificial-tear use as a covariate, with no significant impact on trial results identified in those studies.

This illustrates that background artificial-tear use does not necessarily prevent assessment of a treatment effect, but it should be considered deliberately as part of the study design. Where patients were not using artificial tears before enrollment, introducing a new background treatment during the trial could itself introduce an additional source of variability.

Concomitant medication management also extends to washout and prohibited medications. Washout requirements and permitted treatments should be defined prospectively, with consideration of whether a concomitant therapy could influence the clinical measures being assessed. Treatments affecting similar biological or clinical pathways as the investigational product may require particular consideration.

For sponsors, vehicle response, background treatment and concomitant medication decisions should be considered together during protocol development. Each can influence the conditions under which the investigational treatment is evaluated, making these decisions part of the study design rather than issues to be addressed reactively during study conduct.

Standardized execution is essential to generating consistent clinical data

A well-designed protocol provides the framework for a clinical trial, but the quality of the resulting data also depends on how consistently assessments are performed. Variability in assessment can affect data reliability and make it more difficult to distinguish treatment effects from variation arising from the conduct of the trial.[3]

The recent Fortrea supported DES trial illustrates how these sources of variability can be managed through standardized procedures, appropriate training and prospective planning of operational requirements.

Repeated Schirmer testing provided a clear example of how differences in assessment conditions can affect measurement consistency. The study team standardized key aspects of the procedure, including assessment personnel, operating procedures, testing time frames and environmental conditions, while also defining how measurements extending beyond the standard test range should be handled.

Consistency also depends on when and in what order assessments are performed.[6] In the recent trial, the sequence of ophthalmic examinations was predefined, with best-corrected visual acuity (BCVA) assessed first and intraocular pressure (IOP) last. A defined waiting period was also incorporated for post-treatment visual acuity assessment, while CFS was assessed more than two minutes after fluorescein instillation.

These considerations illustrate that endpoint standardization extends beyond defining what is measured. The conditions under which an assessment is performed can also influence the resulting data.

For multicenter DES trials, operational consistency needs to extend across personnel, procedures, timing, supplies, equipment and environmental conditions. Clear instructions for handling unusual or out-of-range results can also help reduce reliance on individual interpretation.

Operational feasibility should therefore be considered alongside protocol design. Assessment procedures need to be practical for sites to implement consistently, personnel need to be appropriately trained and operational scenarios that could affect measurement should be anticipated before study initiation.

For sponsors, endpoint standardization should extend beyond defining what is measured to specifying how, when and under what conditions it is assessed. The objective is not to eliminate every source of variability, but to identify and standardize those factors that can reasonably be controlled, helping ensure that the data generated during study conduct are as consistent as the protocol intends.



Stratification can help manage important baseline differences

Even with clearly defined eligibility criteria, patients entering a DES trial may differ in the severity and pattern of their symptoms and clinical findings.[1,6] Differences in symptom severity and clinical measures may remain within the eligible population and can contribute to variability in treatment outcomes.[1,6]

Baseline symptom and clinical measures were used to inform stratification, helping to account for relevant variability within the study population and maintain balance between treatment groups.

Together, these factors represented both patient-reported symptoms and objective clinical findings. Their use illustrates how information collected during screening can inform randomization within an otherwise eligible study population.

Stratification should be considered as part of the overall study design, with proposed factors reflecting the study population and clinical question while also being practical to assess consistently at randomization.

For sponsors, important baseline variability should be considered early, with eligibility criteria, randomization and statistical analysis designed as connected elements of the trial. The aim is not to eliminate differences between patients, but to identify baseline characteristics that may be relevant to treatment evaluation and determine how they should be accounted for in the study design.

Putting the principles into practice: Lessons from the recent DES trial supported by Fortrea

The principles described in this paper are grounded in practical experience from a recently completed DES trial conducted by a biotechnology company in China, with Fortrea supporting trial execution. The study brought together the clinical, statistical and operational considerations discussed above, with several practical challenges emerging during study planning and conduct.

Rather than treating these as isolated issues, the study team considered them as interconnected elements of the overall trial design.

Translating protocol requirements into consistent execution

The variability observed in repeated Schirmer testing provided a clear example of how operational execution could affect assessment consistency. The study team addressed this by using a consistent group of assessment personnel, defining operating procedures and testing time frames and considering environmental conditions such as temperature and humidity. A practical issue also arose when patients reached the end of the 30 mm Schirmer strip scale during the five-minute assessment; a 35 mm strip was used, with a defined method for measuring the additional length using a steel ruler.

Other ophthalmic assessments were also standardized prospectively. The examination sequence was predefined, with BCVA assessed first and IOP last, while CFS was assessed more than two minutes after fluorescein instillation.

Together, these examples illustrate how the trial translated protocol requirements into consistent procedures across assessments and sites.

Managing patient selection in practice

The trial also demonstrated the need to combine predefined eligibility criteria with appropriate clinical judgment.

Patients were required to have moderate-to-severe disease, with eligibility criteria incorporating EDS, CFS, Schirmer test results and consistent slit-lamp findings. Symptoms also needed to have been present for at least six months.

Corneal epithelial defects presented further screening consideration. Rather than treating the presence of a defect as an automatic exclusion, the study considered whether it was clinically significant, related to DES and required intervention. Where treatment was necessary and could affect patient safety or evaluation of the investigational treatment, the patient was excluded.

This provided a practical framework for maintaining a defined study population while allowing individual clinical findings to be considered in context.

Managing control and background treatment

Concomitant medication management was another practical consideration. Review of medication histories was important for assessing compliance with washout requirements and identifying prohibited treatments.

At the same time, artificial tears were permitted under defined conditions, including participants in the placebo group, and their use was considered in the analysis. Experience from completed Phase III trials in the United States using the same protocol also provided relevant context: Artificial-tear use was included as a covariate, with no significant impact on the trial results identified.

The completed study also provided internal observations on the response under control conditions. The study observed measurable improvements in some participants receiving placebo, highlighting the importance of considering control-group response when interpreting treatment effects.

Connecting clinical and statistical design

The trial also demonstrated the practical connection between baseline assessment and statistical design. Baseline anesthetized Schirmer test score, EDS and inferior CFS were used as stratification factors for randomization and statistical analysis.

This meant that information collected during screening served more than one purpose: It helped define the study population while also informing how relevant baseline differences were considered in randomization and analysis.

What the trial experience adds

The value of this experience is not that a single DES trial provides a universal solution to trial design. Rather, it shows how relatively small decisions can have implications across different parts of a study.

In this trial, assessment methodology, patient selection, background treatment, control-group response and statistical design were interconnected. Decisions made in one area could affect how consistently data were generated or how treatment effects were interpreted.

For sponsors, the practical lesson is to identify these connections during protocol development rather than treating each issue as a separate operational decision.



Sponsor checklist: Designing a DES clinical trial

Before initiating a DES clinical trial, sponsors can use the following questions to review the overall design and identify potentially avoidable sources of variability.

Sponsor checklist	
Patient selection	• Is the intended disease severity clearly defined? • Do eligibility criteria incorporate relevant symptoms and clinical signs? • Is disease duration relevant? • Are potentially important clinical findings clearly addressed? • Are screening assessments sufficiently standardized?
Endpoint strategy	• Does each endpoint address a defined clinical question? • Are objective and patient-reported measures appropriately considered? • Is the endpoint aligned with the intended treatment effect? • Are assessment procedures, timing and sequence clearly defined?
Control and concomitant treatment	• Could the vehicle influence the signs or symptoms being measured? • Which medications require washout? • Which concomitant therapies should be permitted, prohibited or restricted? • How will background treatment be documented and considered in the analysis?
Operational execution	• Can sites perform the required assessments consistently? • Are personnel appropriately trained? • Are timing, sequence and environmental conditions defined where necessary? • Are supplies and equipment standardized where appropriate? • Are procedures established for unusual or out-of-range results?
Statistical design	• Which baseline characteristics may contribute to variability? • Should relevant symptom or clinical measures be used as stratification factors? • Are proposed stratification factors practical to apply at randomization? • Are clinical and statistical design decisions aligned?

The purpose of this checklist is to identify potentially avoidable sources of variability before they become operational issues during study conduct.

Fortrea: Translating DES trial design into execution

Practical experience is particularly valuable when translating a clinical protocol into consistent execution across study sites.

The recent DES trial by a biotechnology company in China with support from Fortrea illustrates how scientific, statistical and operational considerations can intersect during study conduct. Assessment variability, concomitant medications, background artificial-tear use, ophthalmic assessment procedures and baseline characteristics each required practical decisions beyond the initial protocol design.

For sponsors, this highlights the importance of identifying potential sources of variability before they become operational issues during study execution.

Fortrea's experience supporting ophthalmology clinical trials can contribute practical knowledge of the disease area and its assessments during study planning and execution, helping you anticipate operational challenges and translate protocol requirements into consistent site procedures.

For DES clinical development, this integrated perspective can help maintain alignment between protocol design, clinical assessment, statistical planning and study execution.

Want to learn more?

Get more information and get in touch with the Ophthalmology team at fortrea.com

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