Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

Summary: Clinical trial design report

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Novack GD, Asbell P, et al.: TFOS DEWS II Clinical Trial Design Report. Ocul Surf 2017;15(3): 629-49.

A large number of clinical trials have been conducted to evaluate novel agents for the management of dry eye, yet very few products have been approved to date. The *Clinical Trial Design* report subcommittee reviewed previous studies and elaborated on the challenges faced when designing and conducting dry eye studies and when submitting those for regulatory approval.

Lack of correlation between symptoms and signs

Dry eye is a complex clinical condition, accompanied by ocular symptoms and clinical signs. The complexity of the disease, with a lack of correlation between signs and symptoms, provide a challenge to the set-up, design, outcome and regulatory approval of the study. The subcommittee acknowledges that there seems no obvious single reason as to why so many clinical studies failed to show a benefit of the tested therapy/agent other than that lack of correlation between symptoms and signs.

Flawed study outcome variables

When setting up a clinical study, the subcommittee urges to consider first the mechanism of action of the product and the study phase, and then to decide on the study outcome variables, appropriate study design, study length, inclusion/ exclusion criteria and sample size. For example, when deciding how long participants are to be exposed to the test product, it must be considered how the product works and how long it takes to be effective.

Study outcome variables, which hold the key to determining whether the product is effective or not, should include minimally invasive objective metrics, which correspond to the process of how the novel agent produces its effect. The development of novel ways to assess dry eye, such as biomarkers, is urgently needed and may improve study designs and assessment of efficacy.

Careful consideration of participant pool

Careful consideration has to be given to the number of study participants and the characteristics of those participants (dry eye type, status, severity etc.). Studies with insufficient numbers of study participants may fail to show a difference between the test and control product.

Statistical analysis demands only one data point per observation per participant. For example, tear film break-up data for the right and the left eye of the same participants accumulate to two data points for the same observation, and must be handled appropriately. A large number of clinical studies have overcome this problem by using measurements from one eye only. However, the subcommittee cautions about such an approach, as inter-eye variability for measures such as osmolarity give insight into the dry eye status and are lost with the 'one-eye approach.'

Meeting regulatory standards

In order to bring new products to the market, the study does not only have to show safety and efficacy of the product but has to meet regulatory expectations. Independent of where the study is conducted and which regulatory body shall approve the new product, in order to be considered, the study needs to meet the standards of Good Clinical Practice (GCP). Additionally, to ensure participant and later patient safety, the product quality needs to be in compliance with Good Manufacturing Practice (GMP).

While these requirements are common across the regulatory bodies in different areas of the world, other requirements for approvals differ. For example, the regulatory body in the USA (FDA) demands that two independent clinical studies show efficacy in both, symptoms and signs in the same trial. Considering the lack of correlation between signs and symptoms, many studies have failed to show such efficacy. The FDA recently acknowledged this challenge and allowed the demonstration of efficacy on signs and symptoms in different trials for a product approval. While the FDA will consider either, a negative-control study (superiority of the test product required) or a positive-control study (test product must be at least as effective as the control product), in Europe, a positive-controlled study against an approved product is required for approval. Such differences must be considered when designing and planning clinical studies in dry eye.

Adherence to GCP and GMP, and compliance with standards based on product development phase and compliance with good trial design as recommended in this report should lead to improvements in study outcomes and hopefully approval of more products.

REFERENCES

Novack GD, Asbell P, et al.: TFOS DEWS II Clinical Trial Design Report. *Ocul Surf* 2017;15(3): 629-49.