

Designing a Clinical Trial for Glaucoma Treatments

Which endpoints should be used?

BY MICHAEL WAISBOURD, MD; LISA A. HARK, PhD, RD; AND L. JAY KATZ, MD

In 2010, participants at the National Eye Institute-Food and Drug Administration Glaucoma Clinical Design and Endpoints Symposium (NEI-FDA) discussed the adoption of new endpoint measures for assessing glaucoma therapies in clinical trials. Currently, the FDA generally accepts IOP and visual field (VF) endpoints for evaluating new treatments for glaucoma.

STRUCTURAL AND FUNCTIONAL ENDPOINTS

Because structural changes (eg, changes detected by optical coherence tomography or stereoscopic disc photographs) may predict VF outcomes,¹ discussion continues on whether or not these should be included as valid endpoints in clinical trials. In the Ocular Hypertension Treatment Study (OHTS), 52% of eyes reached only an optic disc endpoint, 24% reached only a VF endpoint, and 24% reached an endpoint by both VF and optic disc criteria.² These results highlight the importance of using structural changes to evaluate glaucomatous progression. Because the loss of 25% to 35% of retinal ganglion cells is associated with abnormal VF testing,³ a structural measure could predict future functional change. According to the FDA, however, prior to the adoption of structural endpoints for glaucoma therapy trials, a strong correlation with vision loss needs to be established.⁴

COMPOSITE ENDPOINTS

A composite endpoint (CEP) is composed of multiple single endpoints that have been combined together to form one outcome measure. The CEP is achieved as soon as any one of its endpoints occurs.

The major advantage of using a CEP when designing clinical trials is that doing so increases the number of events occurring, thereby reducing the sample size or the time required to observe a specified number of events. This methodology often allows for a more rapid and less

costly clinical trial.⁵⁻¹⁰ A CEP study design may also estimate the net clinical benefit of a therapy and avoid the need to choose a single primary endpoint when many may be of equal importance.⁵

Still, a CEP study design may have several disadvantages. It may be difficult to interpret the results when CEPs are not equally important. There is also the possibility of masking the effects of potentially harmful outcomes associated with an experimental intervention. Sponsors, patients, investigators, the Institutional Review Board, and federal agencies such as the FDA therefore may not approve including CEPs in clinical trials.

COMBINED SAFETY AND EFFICACY SCORE

Traditionally, efficacy and safety outcome measures are presented separately when investigators report clinical trial results in peer-reviewed journals. Should a study design include a combined safety and efficacy score to evaluate a surgical procedure? If such a combined score could be validated, industry might embrace it, because it would allow a more economical study design. Patients could have access to the score, and physicians would be able to rapidly interpret the role of the device investigated. The FDA might also be able to streamline its evaluation and approval process.

A combined score could also generate some concerns. Balancing risk versus benefit has been the traditional process, and merging these into a single score might mask important aspects of a device's safety and efficacy profile. Moreover, using a composite efficacy and safety score does not allow direct comparison of scores between studies, which are composed of different populations and use different designs. To compare devices directly, a multicenter, randomized, controlled trial is still the gold standard.

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In addition, a device could be highly effective, but serious side effects would result in a low CEP score (ie, Device A: 95% efficacy and 30% safety = CEP 65% vs Device B: 72% efficacy and 2% safety = CEP 70%). Each device should be available for the targeted population with specific labeling. Because CEP scores are public information, patients may misinterpret this score. A patient who had poor results using Device A and found out that Device B had a higher CEP score might feel misled, yet Device B might not have been the ideal choice for this patient.

CONCLUSION

Glaucoma may be too complex to use a truly meaningful CEP score. Change in disease severity, rapidity of progression, adherence to medications, life expectancy, and quality of life are all factors in real-life decision making and may minimize the impact of CEP scores. Specific outcome measures for glaucoma in clinical trials such as targeted IOP reduction, VF score and progression, and structural parameters for disease identification and deterioration remain difficult to define, but there has been considerable progress in building outcome measures that are meaningful and acceptable to the medical community. ■

Lisa A. Hark, PhD, RD, is director of the Glaucoma Research Center at the Wills Eye Hospital in Philadelphia. Dr. Hark may be reached at (215) 928 0345; lhark@willseye.org.



L. Jay Katz, MD, is director of the Glaucoma Service at the Wills Eye Hospital and professor of ophthalmology at Thomas Jefferson University, both in Philadelphia. Dr. Katz may be reached at (215) 928-3123; ljkat@willseye.org.



Michael Waisbourd, MD, is research manager at the Wills Eye Hospital in Philadelphia. Dr. Waisbourd may be reached at (215) 928-3123; mwaisbourd@willseye.org.



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