The American Academy of Ophthalmology Task Force for Developing Novel Endpoints for Premium Intraocular Lenses Members include Jack Holladay, MD, Chair; Adrian Glasser, PhD, Co Chair, Scott MacRae, MD, Co Chair, Samuel Masket, MD, Walter Stark, MD, and the following FDA staff members: Malvina Eydelman, MD, Don Calogero, MS, Gene Hilmantel, OD, Eva Rorer, MD, Tieuvi Nguyen, PhD, and Michelle Tarver, MD, PhD.

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# Special Report: American Academy of Ophthalmology Task Force Consensus Statement for Extended Depth of Focus Intraocular Lenses

With the advent of wavefront technology, our clinical understanding of human optics and visual performance allows intraocular lens (IOL) manufacturers to manipulate lens design to optimize our visual world. These specially designed extended depth of focus (EDF) lenses use optics that increase depth of focus, potentially allowing better intermediate vision while minimally affecting distance vision. The tradeoff with use of EDF lenses is a reduction in distance image quality if the aberration magnitude is too large.

The American Academy of Ophthalmology Task Force Consensus Statement on EDF IOLs provides criteria to evaluate the implant performance under photopic, mesopic, and glare conditions. The criteria define minimum performance levels to categorize the device as an EDF IOL based on testing at distance, intermediate, and defocus curve testing. The consensus statement also provides recommendations on defocus curve testing methodology, lighting conditions, and the use of digitized charts with randomized presentation of test letters. Implementation of these recommendations will improve the sensitivity of testing and provide more objective data for the U.S. Food and Drug Administration and clinicians.

Intermediate vision and varied lighting conditions have become more critical with the advent of smartphones, tablets, and desk computers. Concise objective testing of patients implanted with EDF IOLs using intermediate tasks will enable us to understand how these lenses perform under these circumstances.

The human visual system is an elegant optical system that provides less-than-perfect images within our neural system. Our neural system then modifies and interprets the images based on past experiences to optimize our performance in daily activities. Understanding the relationship between optics and visual performance of EDF IOLs allows clinicians to guide our patients wisely on the advantages and limitations of such lenses. The information that follows will provide a consensus statement for EDF clinical studies to evaluate the clinical performance of patients receiving these IOLs.

## Consensus Statement

The criteria for EDF IOLs are as follows:

The EDF IOL group should consist of a minimum of 100 patients. The control group cohort should be similar for comparisons. The EDF IOLs need to demonstrate comparable monocular mean best-corrected distance visual acuity (BCDVA).

The monocular depth of focus for the EDF-implanted eyes needs to be at least 0.5 diopters (D) greater than the depth of focus for the monofocal IOL controls at logMAR 0.2 (20/32) (see Defocus Curve Testing Methodology, below).

The mean (logMAR) monocular distance-corrected intermediate visual acuity (DCIVA) should be tested under photopic conditions at 66 cm at 6 months and should demonstrate statistical superiority over the control (1-sided test using significance of 0.025).

The EDF IOL needs to have at least 50% of eyes achieving monocular DCIVA of better than or equal to logMAR 0.2 (20/32) at 66 cm. A logMAR visual acuity chart in 0.1 log unit steps should be used (e.g., ETDRS chart) as designed for the intermediate distance testing.

The EDF IOL needs to demonstrate comparable monocular mean BCDVA to the monofocal controls through a statistical noninferiority analysis, using a noninferiority margin of 0.1 logMAR (1-sided test using significance level of 0.05).

There are additional considerations in the testing of EDF IOLs, including those described below.

## Lighting Conditions

All vision testing should be performed with dark or dim ambient lighting conditions. In addition, ambient lighting must not affect the background luminance of the chart (incident on the chart) or be directed at the patient (providing an additional glare source). No light source should detract from the appearance of the chart to the patient (i.e., glare or distracting reflections should be avoided), and no light source should be visible to patients other than the chart illumination.

## Defocus Curve Testing Methodology

A monocular defocus curve should be obtained by using the best-corrected distance refraction and measuring the visual acuity between +1.50 D and −2.50 D in 0.5-D defocus steps, except in the region from +0.50 D through −0.50 D, which should be done in 0.25-D steps. Letters should be randomly presented to avoid memorization. The defocus range of +1.50 D to −2.50 D may be modified as applicable based upon lens design and expected depth of focus. The protocol should specify the specific defocus range and steps to use.

The mean acuity across all eyes (in a study arm) should be calculated and plotted. The "depth of focus" is defined as the range of lens powers (from zero defocus to the largest negative power) over which the mean acuity is 0.2 logMAR (20/32) or better. ANSI/ISO-compliant visual acuity charts should have a recom-mended nominal luminance of 85 cd/m$^2$ (80−100 cd/m$^2$) with letters changed randomly between each change in trial lens power.

The mean, standard deviation, and confidence intervals for each point on the curve should be reported.

Pupil diameter should be measured with the defocus curve measurements. It is recommended that the pupil size be measured on the same day the defocus testing is performed and under the same photopic light conditions as the test. The defocus data are affected by pupil size and axial length, which must also be recorded. The data should be stratified into small (<3.0 mm), medium (≥3.0 to ≤4.0 mm), and large (>4.0 mm) pupils and short (<21.0 mm), medium (≥21.0 to ≤26.0 mm), and long (>26.0 mm) eyes. Stratified analyses of "depth of focus" and defocus curve plots should evaluate the effect of pupil size and axial length.

## Mesopic Contrast Sensitivity Testing

Testing must be performed with and without glare.

Tests with gratings that avoid rotational bias (vertical or horizontal) may increase the sensitivity of the testing. If linear gratings are used, the ends of the gratings must be blurred (e.g., Gabor filter) to avoid edge detection. The contrast of the gratings should use the Michelson definition (High − Low)/(High + Low) and maintain an average spatial luminance of 2.7 cd/m$^2$ for mesopic conditions. At 100% Michelson contrast, the High would be 5.4 cd/m$^2$ and Low would be zero. At 50% Michelson contrast, the grating High would be 4.05 cd/m$^2$ and Low would be 1.35 cd/m$^2$: (4.05 − 1.35)/(4.05 + 1.35) = 2.70/5.40 = 50%. Mesopic light levels can be achieved by using 1.5 neutral density filters, which results in a recommended nominal mesopic luminance of 2.7 cd/m$^2$ (2.5−3.2 cd/m$^2$) (based on the photopic luminance level described above).

The mesopic contrast sensitivity function should be performed at 4 nominal spatial frequencies: 1.5, 3.0, 6.0, and 12.0 cyc/deg. (For reference, photopic contrast sensitivity function is performed at 3.0, 6.0, 12.0, and 18.0 cyc/deg.) The use of digitized charts is recommended, as they may aid with sensitivity and randomization of the grating presentations.

A small validation study should be performed to confirm that the glare parameters used are the minimum necessary to reduce significantly (e.g., 0.1 log units at 1 or more of the 4 specified spatial frequencies) the contrast sensitivity of young adult subjects with normal vision and no pathology.

## Intermediate-Vision Low-Contrast Acuity at 66 cm (Distance Corrected)

To help assess the quality of distance and intermediate vision under suboptimal conditions, monocular 10% contrast (using the Weber definition: [background − optotype]/background) letter acuity (DCIVA) at photopic light levels should be measured on each subject. Using the Weber contrast definition, the optotype luminance would be 76.5 cd/m$^2$ with the photopic background luminance at 85 cd/m$^2$: (85 − 76.5)/85 = 8.5/85 = 10%. The EDF and monofocal control eye testing should be done with best distance-corrected monofocal vision tested first at distance and then at intermediate (tested at 66 cm). Descriptive statistics (mean, standard deviation, median, maximum, and minimum) should be provided for each arm, comparing test eyes with controls.

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# Special Report: American Academy of Ophthalmology Task Force Recommendations for Specular Microscopy for Phakic Intraocular Lenses

The American Academy of Ophthalmology Task Force Consensus Statement on Specular Microscopy for investigational phakic intraocular lenses provides more detail than currently available guidelines on the management of specular microscopy evaluations to ensure subject safety during the clinical investigation of new phakic intraocular lenses (PIOLs). Although these recommendations were written for PIOLs, similar safety principles could be used for pseudophakic intraocular lenses in studies that require subject follow-up for similar or shorter durations. Specular microscopy is an important prognostic test that allows clinicians to identify unacceptable progressive corneal endothelial cell loss rates and potentially remove an offending implant before the damage causes irreversible corneal edema.[1] These studies are critical not only to demonstrate the overall safety of the device being evaluated for the general population but also to protect participating study subjects.[2,3]

Although current American National Standards Institute (ANSI) guidelines exist for PIOL studies, these do not describe how the investigators should be notified and how they should follow subjects showing significant losses during the trial. Therefore, we have specified some recommendations concerning how information should pass between sponsors of such new PIOLs, reading centers, and the investigations, so that subject safety is adequately protected.

## Consensus Statement

### Endothelial Cell Data

Specular microscopy should be performed preoperatively and at the 6-, 12-, 24-, and 36-month postoperative intervals (at a minimum). A minimum of 6 scans with good images should be performed at the preoperative visit and a minimum of 3 scans with good images should be performed at each postoperative visit. Care should be taken to minimize artifacts caused by dry eye or a poorly focused image. The proportion of eyes with $\geq$25% endothelial cell loss from preoperative cell density should be considered an end point for a clinical investigation of a new PIOL.

A $\geq$20% endothelial cell loss or an endothelial cell count of $<$1500 cells/mm$^2$ should trigger recalling the subject and retesting the specular microscopy to confirm the cell loss or count.[1] Serial specular microscopies can be performed on eyes of concern every 4 to 6 months to evaluate the cell density stability. For these eyes, if there appears to be an accelerated annual cell loss rate above 1%/year, then implant removal may be considered.

The reading center should read the specular microscopy images and report the cell count in cells/mm$^2$ to the sponsor of a clinical investigation within 90 days of when specular microscopy is performed, so that the sponsor can analyze the percentage increase or decrease in cell density compared with preoperative readings. The sponsor should notify the investigator within 30 days of receiving a reading center report if the endothelial cell density decreases 20% or more from the preoperative value or falls below 1500 cells/mm$^2$. The sponsor should also report annually to the investigator any eyes that have a 15% or higher cell density decrease from the preoperative value.

Specular microscopy imaging systems using validated manual counting methods are currently standard for such studies. The ANSI Z80.13 Phakic Intraocular Lenses standard (clause D.4.2) provides detailed recommendations to minimize the variability of specular microscopy measurements.

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