DRAFT CONSENSUS STATEMENT FOR COMMENT
October 9 2015

This statement was developed as a result of breakout group recommendations from the March 24, 2014 Developing Novel Endpoints for Premium IOLs Workshop held in Silver Spring, Maryland. The primary goal of the workshop was to improve the regulatory science for evaluating premium IOLs, which in turn may enhance the efficiency with which safe and effective premium IOLs get to the market.

We are indebted to the Task Force on Developing Novel Endpoints for Premium IOLs formed after the Workshop for developing these statements based on the workshop discussions and recommendations, available peer-reviewed scientific literature, and other expert opinions. The Task Force includes the following: Jack Holladay, MD, Chair; Adrian Glasser, PhD, Scott MacRae, MD, Samuel Masket, MD, and Walter Stark, MD. The FDA liaisons to this Task Force include the following: Malvina Eydelman, MD, Don Calogero, MS, Gene Hilmantel, OD, MS, Tieuvi Nguyen, PhD, RAC, Eva Rorer, MD, and Michelle Tarver, MD, PhD.

We would like to solicit broad input from industry and other interested parties.

Please send your comments, your affiliation and contact information with the title of the referenced document to hoskinscenter@aao.org by the following deadline: **November 10, 2015** Please note that comments received after close of the comment period will not be accepted.

Foreword

In 1978, the US Food and Drug Administration (FDA) approved the first investigational device exemption (IDE) trials of intraocular lenses (IOLs). Outcomes were initially published in 1983 on pooled, publicly available data from IOL IDE trials that were used to support marketing approvals (Stark WJ, et al. The FDA Report in Intraocular Lenses. Ophthalmology 1983; 90:311-317). After this publication, this "historical control" information was used for the assessment of the safety and effectiveness of new IOLs. Over time, these safety and effectiveness endpoints have been referred to as the "FDA Grid" and "Safety and Performance Endpoints" (SPEs) for IOLs and have been modified and updated to certain extents on several occasions. The most recent iteration comes from the ISO and may be noted in the table. (International Organization for Standardization. Geneva, Switzerland: ISO 11979-7:2014 Ophthalmic implants – Intraocular Lenses - Part 7: Clinical investigations; 2014)

Table

Current Adverse Event (AE) SPE Rates for Posterior Chamber Intraocular Lenses and Anterior Chamber Intraocular Lenses per International Organization for Standardization

Cumulative AEs	PCIOL	ACIOL
Endophthalmitis (defined as inflammatory reaction, sterile or infectious, involving the vitreous body)	0.1%	0.2%
Lens dislocated from posterior chamber/anterior chamber	0.1%	1.1%
Pupillary block	0.1%	2.0%
Hypopyon	0.3%	0.2%
Retinal detachment	0.3%	1.2%
Secondary surgical intervention (excludes posterior capsulotomies)	0.8%	2.6%
Cystoid macular edema	3.0%	10.0%
Persistent AEs		
Corneal stroma edema	0.3%	0.5%
Iritis	0.3%	0.9%
Increased IOP requiring treatment	0.4%	2.1%
Cystoid macular edema	0.5%	3.8%

ACIOL = anterior chamber intraocular lens; AE = adverse event; IOP = intraocular pressure; PCIOL = posterior chamber intraocular lens.

IOL technology has progressed markedly since inception and the initial "grid" might be either inappropriate or incomplete with respect to more current IOLs, particularly those considered as

"Premium" IOLs. The latter include diffractive and refractive multifocal IOLs, accommodative IOLs, IOLs for correction of astigmatism, and phakic IOLs for ametropia. A new category of IOL, "Extended Depth of Focus," was publicly introduced at the FDA/American Academy of Ophthalmology (AAO) Workshop on Developing Novel Endpoints for Premium Intraocular Lenses (Lum F, et al. Special Commentary: Food and Drug Administration and American Academy of Ophthalmology Sponsored: Developing Novel Endpoints for Premium Intraocular Lenses Workshop. Ophthalmology 2015; 122:1522-1531). These IOLs enhance intermediate vision and potentially near vision to a measurable but lesser extent than most multifocal IOLs. Most of the AEs in the "grid" do not have standard definitions and the definitions used could have changed over time with advances in our understanding of ocular pathology. Lacking standard definitions for safety endpoints of Premium IOLs, AAO's Task Force developed consensus definitions for SPEAEs. In general, a one-year time frame is applied for evaluation of pseudophakic lenses and a three-year period for phakic IOLs. Adverse events can be considered as specifically related or unrelated to the investigational device. At this time, acceptable percentages for premium IOL SPE AEs have not been established. However, the definitions below should be used during clinical trials of new IOLs going forward to allow for the determination of appropriate rates that can be applied in the future.

DRAFT AMERICAN ACADEMY OF OPHTHALMOLOGY TASK FORCE CONSENSUS STATEMENT ON ADVERSE EVENT DEFINITIONS FOR SAFETY AND PERFORMANCE ENDPOINTS

I. Adverse event definitions for Safety and Performance Endpoints

A. Endophthalmitis - Postoperative intraocular inflammation requiring vitreous tap and use of intraocular antibiotics.

B. Toxic anterior segment syndrome (TASS) - An acute, noninfectious inflammation of the anterior segment of the eye that develops within 24 to 48 hours after surgery and is characterized by corneal edema and accumulation of white cells in the anterior chamber of the eye. (Mamalis N, Edelhauser HF, Dawson DG, Chew J, LeBoyer RM, Werner L. Toxic anterior segment syndrome. J Cataract Refract Surg 2006; 32:324--33.)

C. Mechanical pupillary block - Mechanical pupillary block represents a shallowing of the peripheral and/or central anterior chamber with or without elevation of IOP by obstruction of the flow of aqueous humor from the posterior chamber through the pupil to the anterior chamber. This may be induced by the crystalline lens, vitreous face, or implanted devices

D. Chronic anterior uveitis - persistent anterior segment inflammation characterized by grade 1+ cell or greater (using the SUN criteria: Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005 Sep;140(3):509-16.) persistent for greater than 3 months after surgery, or relapses in less than 3 months after discontinuation of therapy, or the subject is maintained on therapy for more than 3 months to control inflammation.

E. Corneal edema - which results in a reduced Best Corrected Distance Visual Acuity (BCDVA) of 20/40 or worse at Form 3 (1-month visit) or later

F. Rhegmatogenous retinal detachment

G. Raised IOP - Elevation of IOP $\geq$ 10 mmHg above the baseline and to a minimum of 25mmHg

H. Clinically significant cystoid macular edema - Macular edema diagnosed by clinical exam and adjunct testing (e.g., OCT, fluorescein angiography or other method) and which results in reduced BCDVA to 20/40 or worse at Form 3 (1 month visit) or later.

II. Categorization of Secondary Surgical Interventions:

A. Exchange - exchanged with same investigational IOL due to:

1. Incorrect Power

2. Optic degradation (degradation of optical performance for reasons such as vacuoles, microvacuoles, subsurface nanoglistenings, opacification, cellular adhesion, etc.)
3. Mechanical failure
4. Malpositioned IOL (Please See Task Force Consensus Statement on Measurement of Tilt, Decentration and Chord Length MU)
    a. Early[1] - include capsule block syndrome
    b. Late[2]
5. Post YAG Event

B. Reposition of the same IOL due to:
1. Malpositioned IOL (Please See Task Force Consensus Statement on Measurement of Tilt, Decentration and Chord Length MU)
    a. Early[1]
    b. Late[2]
2. Rotation of toric IOLs
3. "Capsule Block Syndrome"
4. Post YAG laser event
5. Patient-reported symptoms related to undesired optical phenomena, e.g., negative dysphotopsia, without malposition of the IOL

C. Rotation due to spontaneous rotation of the IOL that occurred:
1. Early[1]
2. Late[2]

D. Removal - exchange with already marketed IOL or no IOL was implanted after removal – due to:
1. Incorrect power
2. Patient-reported symptoms related to undesired optical phenomena: negative and positive dysphotopsia, monocular diplopia, glare, halos, etc.
3. Optic degradation
4. Mechanical failure
5. Malpositioned IOL
    a. Early[1]
    b. Late[2]
6. Post YAG laser surgery event
7. Cataract formation (for phakic IOLs) - development of an opacity or translucency of the crystalline lens with or without reduced visual acuity.

[1] Early - prior to Form 4 visit window (i.e., < 120 days)
[2] Late – At 120 days or later

8. Pupil ovalization (for anterior chamber and/or phakic IOLs) - this needs to be measured under controlled photopic conditions (see Attachment A). The larger diameter of the oval pupil should be in the same meridian as the IOL.
9. Loss of pigment endothelium of the iris (for anterior chamber and/or phakic IOLs) - as evidenced by any new iris transillumination defects on retro-illumination and/or pigment cells in anterior chamber after the 1 week postoperative visit assessed before dilation or instillation of any pharmaceutical agents. If there is a transillumination defect preoperatively, then a photograph should be taken, and then at each subsequent visit, a photograph should be taken and compared to the preoperative photograph. If there is a difference, then this would be considered an adverse event. Each sponsor should propose a standardized photographic method.
10. Additional reasons for removal of anterior chamber IOL
    a. Removal for endothelial cell loss
    b. Chronic anterior uveitis
    c. Progressive peripheral anterior synechiae (PAS) – a mechanical PAS may occur in the absence of obvious uveitis
    d. Pain graded as 4 or above on the pain numeric rating scale on which patients rate their current pain intensity from 0 (no pain) to 10 (worst possible pain) (Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. Pain. 1999; 83:157–162.)

Attachment A

Oval Pupil Measurement Background and SOP

Background

The only study of the oval pupil available was by Isotani in 1995 which studied the ratio of the Major to Minor diameter in healthy subjects using infrared photography.[1] The subjects were dark adapted, so these are scotopic pupil measurements. .

Standard Operating Procedure

If the clinician observes an oval or irregularly shaped pupil (dyscoria) at any visit after surgery, photographs should be taken at that visit and each subsequent visit to determine if the ovalization is progressive. The major and minor diameters of the pupil, which may not be orthogonal are measured on the photograph, which must be taken in photopic conditions (> 200 foot-candles or 2153 lux) so the pupil is maximally constricted. For the measurement, the diameters must pass through the center of the least-squares best fit ellipse or centroid of the pupil perimeter. The ratio of the major to minor diameter is then calculated and reported. The photograph may be taken with any camera, including but not limited to slit-lamp cameras, topographers and Scheimpflug devices, but the eye image must be captured under photopic conditions as specified above.

[1] Isotani H1, Fukumoto Y, Kitaoka H, Furukawa K, Ohsawa N, Utsumi T. Oval pupil in patients with diabetes mellitus: examination by measurement of the dark-adapted pupillary area and pupillary light reflex. Diabetes Res Clin Pract. 1995 Jul;29(1):43-8.