Limitations of Existing Endpoints for Premium IOLs

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Disclosure

• No Financial Relationships to Disclose
IDE Study Approval vs. Available Study Recommendations

• **Monofocal IOLs:**
  » FDA recognized ANSI/ISO standards
    ▪ Preclinical and clinical recommendations clearly delineated
  » 71% total IDEs (FY’05-FY’12) were approved or approved with conditions within first round

• **Premium IOLs:**
  » Few recognized ANSI/ISO Standards
    ▪ Several endpoints not clearly delineated
  » 39% total IDEs (FY’05-FY’12) were approved or approved with conditions within first round
Aphakic Monofocal IOL Investigations (ISO 11979-7)

• Effectiveness
  » Best Corrected Visual Acuity (BCVA)

• Safety
  » Safety and Performance Endpoints (SPE)\(^2\) rates for Adverse Events (AEs)
    - corneal edema
    - hypopyon
    - intraocular infection
    - secondary surgical intervention
    - raised IOP requiring treatment
    - cystoid macular edema
    - pupillary block
    - retinal detachment
    - iritis

» IOL tilt / Decentration

\(^1\) FDA Recognized Standard
\(^2\) Basic historical safety and effectiveness data (FDA Grid) incorporated in ISO 11979-7
Phakic Monofocal IOL investigations (ISO 11979-10, ANSI Z80.13)¹

**Effectiveness** – BCVA plus:
- Best Distance Corrected Near Visual Acuity
- Uncorrected Near Visual Acuity (ANSI only)
- Uncorrected Distance Acuity (UCDA)

**Safety** – SPE plus:
- Endothelial Cell Loss
- IOL Tilt / Decentration
- Contrast Sensitivity
- Crystalline lens status
- Clearance analysis (e.g., IOL-cornea)
- Subject Questionnaire
- AEs related to IOL design

¹ FDA Recognized Standards
Aphakic Multifocal IOL Investigations (ISO 11979-9 and ANSI Z80.12)\textsuperscript{1}

**Effectiveness** – BCVA\textsuperscript{2} plus:
- Uncorrected Near VA, Uncorrected Distance VA\textsuperscript{2}
- Distance Corrected Near VA (DCNVA)\textsuperscript{2}
- Defocus curve (depth of focus)\textsuperscript{3}

**Safety** – SPE plus:
- Explants for optical / visual reasons
- Mesopic DCNVA
- IOL Tilt / Decentration
- Contrast sensitivity\textsuperscript{4}
- Fundus visualization
- Functional performance (night driving testing)\textsuperscript{4}
- Subject Questionnaire (visual symptoms/aberrations)\textsuperscript{4}

\textsuperscript{1} FDA Recognized Standards
\textsuperscript{2}, Monocular and Binocular ; \textsuperscript{3} Binocular ; \textsuperscript{4}Outcomes compared to a concurrently run monofocal IOL control group.
Toric IOL Investigations: Aphakic and Phakic
(ISO 11979-7 DIS and ANSI Z80.30)

- **Effectiveness**\(^1\) – BCVA plus:
  - Evaluation of Cylinder
    - refractive cylinder, IOL misalignment, IOL rotational stability, pre-op and postop keratometry
  - UCVA

- **Safety** – SPE plus:
  - IOL Tilt / Decentration
  - Subject Questionnaire (visual symptoms/aberrations)\(^2\)

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\(^1\) Effectiveness Outcomes are compared to those associated with a concurrently run non-toric IOL (similar design) control group for the lowest power only

\(^2\) For ISO only, if necessary based on risk analysis
Aphakic Accommodative Investigations
(ISO 11979-7 DIS and ANSI Z80.30 (Draft))

Effectiveness – BCVA plus:
• Distance, Intermediate, Near UCVA
• Intermediate and Near VA with Best Correction for Distance
• BCNVA and Add Power
• Accommodative Amplitude (AA) (objective testing, 1 D min.) / Assess AA Stability

Safety – SPE plus:
• IOL Tilt / Decentration
• Contrast Sensitivity
• Subject Questionnaire
• AEs related to IOL design
Limitations of Current Standards for Premium IOLs

• Performance Criteria
  » SPE
    ▪ Key safety outcome in all standards
    ▪ Entry of premium IOLs to the marketplace highlight limitations (e.g., different rates of secondary surgical interventions)

• Testing
  » Some recommended tests for “Premium” IOLs do not have well established methodologies
    ▪ IOL tilt/decentration
    ▪ Objective method for anterior subcapsular cataract and posterior capsular opacification
    ▪ Accommodation
    ▪ Functional performance (e.g. reading speed, night driving)
    ▪ Patient Reported Outcomes
Introduction of Extended Depth of Focus (EDOF) IOLs

• New Category of IOLs for Improved Near and Intermediate Performance
• No current standards or draft standards
• No guidance
• Today – the first public discussion of probable requirements for preclinical and clinical testing
Today’s Focus on Areas with Highest Impact

• Premium IOL Safety Assessments
• Patient Reported Outcome (PRO) Measures
• Objective Assessments of Accommodation
• Subjective Assessments of Accommodation and EDOF
Premium IOL Safety Assessment

Concerns with historical adverse event (AE) rates currently used as safety benchmarks:

- May not reflect current standard cataract surgery instrumentation and techniques
- Different types of AEs with premium IOLs
- Acceptable rates of AEs with premium IOLs may be different
  » Different risks/benefits for premium vs. monofocal IOLs
Patient-Reported Outcomes (PROs)

• Concerns with currently used questionnaires
  » Have not undergone psychometric evaluation
  » Have not been evaluated for validity in the intended population
  » Have not robustly shown that the scores are meaningful
  » Have not been developed and evaluated for some concepts of interest
Assessment of Accommodation

• Limitations of subjective assessments:
  » Cannot distinguish true accommodation from pseudo-accommodation
  » Affected by multiple non-specific factors \(\rightarrow\) bias (overestimates)

• Objective assessments – outstanding issues:
  » Optical: Can they be used with all lenses?
  » Biometric: difficulties with ocular fixation, stimulation of accommodation, and conversion to optical diopters
  » Need standardization of procedures?

• ANSI/ISO standards call for objective measurements to minimize limitations of subjective assessments
Subjective Assessment of Accommodation and Extended Depth of Focus (EDOF)

• Concerns with subjective evaluations of accommodation and depth of focus
  » Current subjective methods
    ▪ may not be adequate to differentiate true performance difference from placebo effect (e.g., effects of patient squinting, blur interpretation)
    ▪ may not accurately assess accommodation

• In EDOF subjects - manifest refractions may have high variability

• No current standards or guidance exist to assist in the development of EDOF IOLs
Development of Endpoints for Premium IOLS

The Fastest Route To Market